(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 July 2008 (03.07.2008)

PCT

(10) International Publication Number
WO 2008/079404 A2

(51) International Patent Classification: Not classified

(21) International Application Number: PCT/US2007/026336

(22) International Filing Date: 21 December 2007 (21.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/877,079 22 December 2006 (22.12.2006) US

(71) Applicant *(for all designated States except US)*: **SPHERICS, INC.** [US/US]; 375 Forbes Boulevard, Mansfield, MA 02048-1805 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NANGIA, Avinash** [CA/US]; 4 Salamander Way, Sharon, MA 02067 (US). **JACOB, Jules** [US/US]; 95 Lake Ridge Drive, Taunton, MA 02780 (US). **YEH, James** [US/US]; 9 Maura Elizabeth Lane, Foxboro, MA 02035 (US). **MOSLEMY, Peyman** [CA/US]; 65 Marrow Street, Mansfield, MA 02048 (US). **VERMA, Daya, D.** [IN/US]; 205 Cinder Road, Edison, NJ 08820 (US). **HASWANI, Dinesh, K.** [IN/US]; 7435 Placid Lake Drive, Apt. 311, Mason, OH 45040 (US). **SHAKED, Ze've** [US/US]; 20 Arnold Palmer Drive, San Antonio, TX 78257 (US).

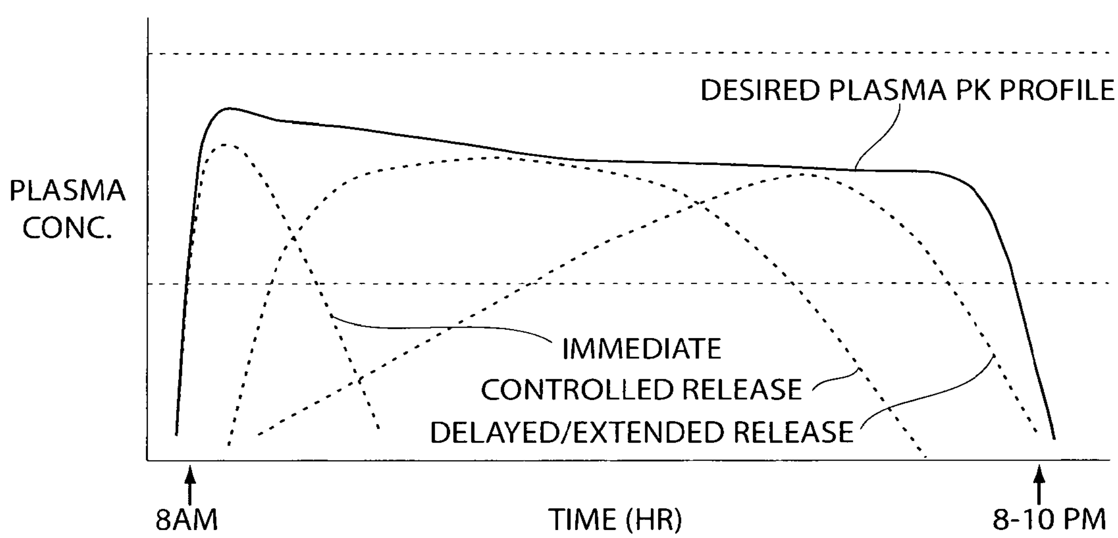
(74) Agents: **VINCENT, Matthew, P.** et al.; Ropes & Gray LLP, One International Place, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR TREATMENT OF PARKINSON'S DISEASE AND RELATED DISORDERS



(57) Abstract: The invention relates to the improvement in the treatment of certain neural disorders / diseases, such as Parkinson's disease and other motor disorders. The invention relates to drug compositions and dosage forms comprising said drug composition; methods of manufacturing the drug compositions and dosage forms; and methods of treatment, comprising administering the drug composition and dosage form to an individual. In certain embodiments, a decarboxylase enzyme inhibitor (e.g., carbidopa) extended release formulation is formulated with one or more bioadhesive polymers which may be useful for preferentially targeting the release of the decarboxylase enzyme inhibitor at the target absorption site. Upon administration to the patient, the inhibitor is delivered to a desired tissue location (e.g., proximal small intestine), and is released over an extended period (preferably from after dinner to the morning after).

WO 2008/079404 A2

Published:
— *without international search report and to be republished upon receipt of that report*

PHARMACEUTICAL COMPOSITIONS FOR TREATMENT OF PARKINSON'S DISEASE AND RELATED DISORDERS

Reference to Related Applications

This application claims the benefit of the filing date of U.S. Provisional Application No. 60/877,079, filed on December 22, 2006, the entire content of which is incorporated herein by reference.

Many relevant Examples, formulations, drug delivery devices, tablets, dosage profiles, etc. are described in the co-owned PCT application No. PCT/US2006/024663, filed on June 23, 2006 (now published as WO 2007/002516). The entire content of WO 2007/002516 (including all the examples, figures and tables therein) is incorporated herein by reference.

Background of the Invention

A movement disorder is a neurological disturbance that involves one or more muscles or muscle groups. Movement disorders affect a significant portion of the population, causing disability as well as distress. Movement disorders include Parkinson's disease, Huntington's chorea, progressive supranuclear palsy, Wilson's disease, Tourette's syndrome, epilepsy, tardive dyskinesia, and various chronic tremors, tics and dystonias. Different clinically observed movement disorders can be traced to the same or similar areas of the brain. For example, abnormalities of basal ganglia (a large cluster of cells deep in the hemispheres of the brain) are postulated as a causative factor in diverse movement disorders.

Parkinson's disease is a movement disorder of increasing occurrence in aging populations. It is a progressive neurodegenerative disorder affecting the mobility and control of the skeletal muscular system. The disease is associated with the depletion of dopamine from cells in the corpus striatum. Parkinson's disease is a common disabling disease of old age affecting about one percent of the population over the age of 60 in the United States. The incidence of Parkinson's disease increases with age and the cumulative lifetime risk of an individual developing the disease is about 1 in 40. Symptoms include pronounced tremor of the extremities, bradykinesia, rigidity and postural change. A perceived pathophysiological cause of Parkinson's disease is progressive destruction of dopamine-producing cells in the basal ganglia which comprise the pars compartum of the substantia nigra, basal nuclei located

in the brain stem. Loss of dopamineric neurons results in a relative excess of acetylcholine. See Jellinger, *Post Mortem Studies in Parkinson's Disease - Is It Possible to Detect Brain Areas For Specific Symptoms*? *J. Neural. Transm.* **56(Supp)**: 1-29:1999. Parkinson's disease often begins with mild limb stiffness and infrequent tremors and progresses over a period of ten or more years to frequent tremors and memory impairment, to uncontrollable tremors and dementia.

Tardive Dyskinesia (TD) is a chronic disorder of the nervous system, characterized by involuntary, irregular rhythmic movements of the mouth, tongue, and facial muscles. The upper extremities also may be involved. These movements may be accompanied, to a variable extent, by other involuntary movements and movement disorders. These include rocking, writhing, or twisting movements of the trunk (tardive dystonia), forcible eye closure (tardive blepharospasm), an irresistible impulse to move continually (tardive akathisia), jerking movements of the neck (tardive spasmodic torticollis), and disrupted respiratory movements (respiratory dyskinesia). The vast majority of TD cases are caused by the prolonged use of antipsychotic drugs (neuroleptics). A relatively small number are caused by the use of other medications, such as metoclopramide, that, like neuroleptics, block dopamine receptors. TD often manifests or worsens in severity after neuroleptic drug therapy is discontinued. Resumption of neuroleptic therapy will temporarily suppress the involuntary movements, but may aggravate them in the long run.

TD affects approximately 15-20% of patients treated with neuroleptic drugs (Khot *et al.*, *Neuroleptics and Classic Tardive Dyskinesia*, in Lang AE, Weiner WJ (eds.): *Drug Induced Movement Disorders*, Futura Publishing Co., 1992, pp 121-166). Therefore, the condition affects hundreds of thousands of people in the United States alone. The cumulative incidence of TD is substantially higher in women, in older people, and in those being treated with neuroleptics for conditions other than schizophrenia, such as bipolar disorder (manic-depressive illness) (see, *e.g.*, Hayashi *et al.*, *Clin. Neuropharmacol.* **19**: 390, 1996; Jeste *et al.*, *Arch. Gen. Psychiatry* **52**: 756, 1995). Unlike the acute motor side effects of neuroleptic drugs, TD does not respond in general to antiparkinson drugs (Decker *et al.*, *New Eng. J Med.* Oct. 7, p. 861, 1971).

Focal Dystonias (FD) are a class of related movement disorders involving the intermittent sustained contraction of a group of muscles. The prevalence of focal dystonias in one US county was estimated as 287 per million (Monroe County Study); this suggests that at least 70,000 people are affected in the US alone. The spasms of focal dystonia can last many

seconds at a time, causing major disruption of the function of the affected area. Some of the focal dystonias are precipitated by repetitive movements; writer's cramp is the best known example. Focal dystonia can involve the face (*e.g.*, blepharospasm, mandibular dystonia), the neck (torticollis), the limbs (*e.g.*, writer's cramp), or the trunk. Dystonia can occur spontaneously or can be precipitated by exposure to neuroleptic drugs and other dopamine receptor blockers (tardive dystonia). No systemic drug therapy is generally effective, but some drugs give partial relief to some patients. Those most often prescribed are anticholinergics, baclofen, benzodiazepines, and dopamine agonists and antagonists. The most consistently effective treatment is the injection of botulinum toxin into affected muscles.

The various focal dystonias tend to respond to the same drugs (Chen, *Clin. Orthop.* June 102-6, 1998; Esper *et al.*, *Tenn. Med.* **90**: 18-20, 1997; De Mattos *et al.*, *Arq Neuropsiquiatr* **54**: 30-6, 1996). This suggests that a new treatment helpful for one focal dystonia would be likely to be helpful for another. Furthermore, the common symptoms, signs, and responses to medication of spontaneous (idiopathic) dystonia and neuroleptic-induced dystonia suggest that an effective treatment for a drug-induced focal dystonia will be effective for the same dystonia occurring spontaneously.

A tic is an abrupt repetitive movement, gesture, or utterance that often mimics a normal type of behavior. Motor tics include movements such as eye blinking, head jerks or shoulder shrugs, but can vary to more complex purposive-appearing behaviors such as facial expressions of emotion or meaningful gestures of the arms and head. In extreme cases, the movement can be obscene (copropraxia) or self-injurious. Phonic or vocal tics range from throat clearing sounds to complex vocalizations and speech, sometimes with coprolalia (obscene speech) (Leckman *et al.*, *supra*). Tics are irregular in time, though consistent regarding the muscle groups involved. Characteristically, they can be suppressed for a short time by voluntary effort.

Tics are estimated to affect 1% to 13% of boys and 1% to 11% of girls, the male-female ratio being less than 2 to 1. Approximately 5% of children between the ages of 7 and 11 years are affected with tic behavior (Leckman *et al.*, *Neuropsychiatry of the Bas. Gang* **20(4)**: 839-861, 1997). The estimated prevalence of multiple tics with vocalization, *e.g.*, Tourette's syndrome, varies among different reports, ranging from 5 per 10,000 to 5 per 1,000.

Gilles de la Tourette syndrome (TS) is the most severe tic disorder. Tourette's syndrome is 3-4 times more common in boys than girls and 10 times more common in

children and adolescents than in adults (Leckman *et al.*, *Neuropsychiatry of the Bas. Gang* **20(4)**: 839-861, 1997; Esper *et al.*, *Tenn. Med.* **90**: 18-20, 1997). Patients with TS have multiple tics, including at least one vocal (phonic) tic. TS becomes apparent in early childhood with the presentation of simple motor tics, for example, eye blinking or head jerks. Initially, tics may come and go, but in time tics become persistent and severe, and begin to have adverse effects on the child and the child's family. Phonic tics manifest, on average, 1 to 2 years after the onset of motor tics. By the age of 10, most children have developed an awareness of the premonitory urges that frequently precede a tic. Such premonitions may enable the individual to voluntary suppress the tic, yet premonition unfortunately adds to the discomfort associated with having the disorder. By late adolescence/early adulthood, tic disorders can improve significantly in certain individuals. However, adults who continue to suffer from tics often have particularly severe and debilitating symptoms. (Leckman *et al.*, *Neuropsychiatry of the Bas. Gang* **20(4)**: 839-861, 1997).

Although the present day pharmacopeia offers a variety of agents to treat movement disorders, none of these agents can prevent or cure these conditions. Many treatments focus on eliminating or at least alleviating certain symptoms of the disorder. Furthermore, the most effective treatments are often associated with intolerable side effects. There remains a clear-cut need for new treatments for movement disorders that have greater efficacy and fewer side effects than those currently available.

For example, Parkinson's disease (PD) is associated with the depletion of dopamine from cells in the corpus striatum. Since dopamine can't cross the blood brain barrier (BBB), it is ineffective in the treatment of Parkinson's disease. Levodopa, a metabolic precursor of dopamine, readily crosses the BBB, and is metabolically transformed to dopamine by the aromatic L-amino acid decarboxylase enzyme. This enzyme is found throughout the body including gastric juices and the mucosa of the intestine. Thus, treatment with levodopa alone requires administration of large doses of the drug due to extracerebral metabolism by this enzyme. The resulting high concentration of extracerebral dopamine causes nausea in some patients. To overcome this problem, levodopa is usually administered with an inhibitor of the aromatic L-amino acid decarboxylase enzyme such as carbidopa, which cannot itself cross the blood brain barrier and has no effect on the metabolism of levodopa in the brain. The levodopa / carbidopa therapy is considered to be the most effective treatment for symptoms of Parkinson's disease (*The Medical Letter* **35**: 31-34, 1993). Nevertheless, certain limitations become apparent within two to five years of initiating combination therapy. As the disease

progresses, the benefit from each dose becomes shorter ("the wearing off effect"), and some patients fluctuate unpredictably between mobility and immobility ("the on-off effect"). "On" periods are usually associated with high plasma levodopa concentrations and often include abnormal involuntary movements, *i.e.*, dyskinesias. "Off" periods have been correlated with low plasma levodopa and bradykinetic episodes.

A second problem for the multiple dose regimen is that the "peak and trough" blood levels produced by multiple daily doses result in fluctuating stimulation of the dopaminergic neurons. These fluctuations may contribute to the pathogenesis of the motor complications in Parkinson disease. For example, commonly occurring adverse effects associated with MIRAPEX® (a marketed PD drug) include nausea, vomiting / emesis, weakness, dizziness, fainting, agitation, confusion, hallucinations, muscle twitching, uncontrollable movements, a tingling sensation, chest pain, insomnia, somnolence, decreased appetite, dry mouth, sweating, headache, constipation and gastric intestinal complications.

Therefore, there is a need to develop new and improved dosage forms to treat various movement disorders, such as using levodopa / carbidopa in alleviating at least one adverse effect associated with the treatment of Parkinson's disease. Additionally, to the extent that these dosage forms use bioadhesive polymer compositions, there is also a need for improved methods of manufacturing bioadhesive polymer compositions, and for making bioadhesive compositions available at reduced cost.

Summary of the Invention:

The present invention is directed to dosage forms that allow drug to be released in a highly controlled, time-dependent manner.

In general, any of the subject dosage forms and/or delivery devices (such as those described in the figures) may be used to deliver any of a large spectrum of compounds (*e.g.*, drugs, prodrugs, metabolic precursors, *etc.*), especially those with limited absorption windows in upper GI (*e.g.*, stomach).

An exemplary list of compounds that can be delivered using the subject dosage forms and/or delivery devices includes, but not limited to: metformin, acyclovir, ranitidine, riboflavin, chlorthiazide, gabapentin, losartin potassium, ganciclovir, cimetidine, minocycline, fexofenadine, bupropion, orlistat, captopril, diphenhydramine, tripelennamine, chlorpheniramine maleate, promethazine, omeprazole, prostaglandin, carbenoxolane,

sucralphate, isosorbide, quinidine, enalapril, nifedipine, verapamil, diltiazem, nadolol, timolol, pindolol, salbutamol, terbutaline, carbuterol, broxaterol, aminophylline, cyclizine, cinnarizine, domperidone, alizapride, vincristine, megestrol acetate, daunorubicin, actinomycin, adriamycin, etoposide, 5-fluorouracil, indomethacin, sulindac, piroxicam, ibuprofen, naproxen, ketoprofen, temazepam, lorazepam, flunitrazepam, amantadine, ampicillin, amoxicillin, erythromycin, tetracyclines, cyanocobalamin, amino acids, iron or calcium salts of essential trace elements, or pharmacologically acceptable salts of the above.

One aspect of the invention relates in general to any drug that may be used to treat Parkinson's disease (or other movement disorders), especially levodopa / carbidopa therapy using the subject dosage forms and delivery devices.

Preferably, the drugs or prodrugs are released at a rate that results in reduction in the frequency or severity of at least one adverse effect associated with levodopa / carbidopa therapy.

In certain embodiments, the dosage form releases levodopa and carbidopa at a rate that results in reduction in the frequency or severity of at least one adverse event associated with current levodopa / carbidopa therapies, or allows for a more convenient dosing regimen than current therapies.

As used herein, wherever reference to an effective composition (*e.g.*, “levodopa” or “carbidopa”) is made, it should be understood that the effective composition may include drug and/or prodrug. In other words, any drug may be replaced in whole or in part by its prodrug(s), metabolic precursor(s), or analog(s) that provides the same therapeutic effect.

Thus, generally, one aspect of the invention provides a single dosage formulation of a pharmaceutical composition for treatment of a movement disorder. The single dosage formulation comprises levodopa and/or a metabolic precursor thereof, and optionally a decarboxylase enzyme inhibitor, wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa thereof over a period of at least about 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours or more.

In certain embodiments, the pharmaceutical composition comprises: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa or the precursor in the patient within about 2 hours of administration to the patient (*e.g.*, less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to

1 hour, 15 to 20 min., *etc.*) of administration to the patient; (2) a second substantially zero order release portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa or the precursor in the patient; wherein at least the first IR portion further comprises a decarboxylase enzyme inhibitor, and the ratio of the inhibitor to levodopa or the precursor in at least the first IR portion is greater than 1:4.

In certain embodiments, the first immediate-release (IR) portion reaches half-maximum dissolution (*e.g.*, when 50% of the effective composition is released) within about 1 hour, 30 minutes, 15 minutes, 10 minutes, or 5 minutes or less.

In certain embodiments, the pharmaceutical composition further comprises: (3) a substantially ascending release portion comprising levodopa or a metabolic precursor thereof, formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

In certain embodiments, the pharmaceutical composition further comprises: (4) a substantially elevating release portion comprising levodopa or a metabolic precursor thereof, formulated to elevate the substantially zero-order release rate to a higher level beginning around a predetermined time point, such as about 3-7, 4-7, or 4-6 hours after administration to the patient.

In certain embodiments, at the end of the treatment period, the substantially elevating release portion is optionally formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration. This may be effected by, for example, using a similar second immediate-release portion described above.

In certain embodiments, the substantially elevating release portion comprises a decarboxylase enzyme inhibitor.

In certain embodiments, the substantially elevating release portion comprises levodopa or the precursor.

As used herein, "substantially ascending release portion" is an optional portion of the subject single dosage formulation pharmaceutical composition, which release profile resembles a peak, *e.g.*, having sloping ascending and descending slopes with substantially no intervening plateau at which the release is maintained at a substantially constant rate. The ascending and descending slopes of the peak may be, but need not be asymmetrical. In certain embodiments, the ascending slope may be quite steep, *e.g.*, the substantially ascending release

portion may be a second immediate release portion, *e.g.*, as a delayed-release immediate release portion. In other embodiments, the substantially ascending release portion may adopt a substantially milder ascending slope than that of the first immediate release portion, *e.g.*, as a delayed-release controlled-release portion.

As used herein, “substantially elevating release portion” is an optional portion of the subject single dosage formulation pharmaceutical composition, which release profile resembles a plateau, *e.g.*, having an ascending slope, a relatively flat plateau, and a descending slope. The plateau is “elevated,” in that the relative constant level of levodopa is higher than the previous substantially zero-order release rate. The ascending and descending slopes of the peak may be, but need not be, asymmetrical. In certain embodiments, the ascending slope may be quite steep, *e.g.*, the substantially ascending release portion may be a second immediate release portion, *e.g.*, as a delayed-release immediate release potion. In other embodiments, the substantially ascending release portion may adopt a substantially milder ascending slope than that of the first immediate release portion, *e.g.*, as a delayed-release controlled-release portion.

As used herein, “rapid” refers to a time period no more than about 3 hours, 2 hours, 1.5 hours, 1 hour, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes, or less.

In certain embodiments, the various portions of the composition may include multiple drugs, such as carbidopa and levodopa, and their respective prodrugs. The relative proportions of the different drugs or prodrugs may vary at boundaries between the various portions (*i.e.*, different portions may have uniform drug ratios that differ from neighboring components), or may be formulated to change gradually over one or more portions of the composition.

In certain embodiments, the ratio of drug to prodrug (*e.g.*, carbidopa v. carbidopa prodrug; levodopa v. levodopa prodrug, *etc.*) may vary, depending on one or more factors such as relative solubility or other pharmacokinetic properties (*e.g.*, absorption, distribution, metabolism and excretion, *etc.*).

Another aspect of the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of administration to the patient; (2) a second substantially zero order release portion comprising levodopa or a metabolic precursor thereof, formulated

to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient; and (3) a substantially ascending release portion comprising levodopa or a metabolic precursor thereof, formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

Another aspect of the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of administration to the patient; (2) a second substantially zero order release portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient; and (3) a substantially elevating release portion comprising levodopa or a metabolic precursor thereof, formulated to elevate the substantially zero-order release rate to a higher level beginning at a predetermined time point.

Another aspect of the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a sleep-inducing agent; and, (2) a decarboxylase enzyme inhibitor formulated to provide an effective plasma concentration at a predetermined time after the administration of the pharmaceutical composition to the patient.

In certain embodiments, the sleep-inducing agent is benzodiazepine (*e.g.*, LIBRIUM®, VALIUM®), a prescription sleeping aid medicine (*e.g.*, AMBIEN®, RESTORIL®, DESYREL®, and SONATA®), eszopiclone (*e.g.*, LUNESTA™), or a non-prescription (over-the-counter) sleeping aid medicine (*e.g.*, TYLENOL® PM, EXCEDRIN PM®, UNISOM® / NYTOL® / SLEEPINAL®).

In certain embodiments, the pharmaceutical composition is for administration to a patient before sleeping.

In certain embodiments, the pharmaceutical composition is for administration to a patient before sleeping, and the beginning of the delayed immediate release is calculated to begin just prior to the waking of the patient.

In certain embodiments, the pharmaceutical composition further comprises: (3) a first delayed immediate-release (DIR) portion comprising levodopa or a metabolic precursor

thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of the predetermined time.

In certain embodiments, the pharmaceutical composition further comprises: (4) a second delayed controlled release (DCR) portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period after the predetermined time, to maintain the therapeutically effective concentration of levodopa in the patient.

In certain embodiments, the predetermined time after administration is 6 to 9 hours after administration.

In certain embodiments, the rapid drop of levodopa takes place in less than two hours.

In certain embodiments, the formulation further comprises one or more of a dopamine precursor, such as L-dopa; a dopaminergic agent, such as Levodopa-carbidopa (SINEMET®, SINEMET CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a dopaminergic and anti-cholinergic agent, such as amantadine (SYMMETRYL®, SYMADINE®); an anti-cholinergic agent, such as trihexyphenidyl (ARTANE®), benztropine (COGENTIN®), ethopropazine (PARSITAN®), or procyclidine (KEMADRIN®); a dopamine agonist, such as apomorphine, bromocriptine (PARLODEL®), cabergoline (DOSTINEX®), lisuride (DOPERGINE®), pergolide (PERMAX®), pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a MAO-B (monoamine oxidase B) inhibitor, such as selegiline or deprenyl (ATAPRYL®, CARBEX®, ELDEPRYL®); a COMT (catechol O-methyltransferase) inhibitor such as CGP-28014, entacapone (COMTAN®), or tolcapone (TASMAR®); a muscle relaxant, such as baclofen (LIORESAL®); a sedative, such as Clonazepam (RIVOTRIL®); an anticonvulsant agent, such as carbamazepine (TEGRETOL®); a dopamine reuptake inhibitor, such as tetrabenazine (NITOMAN®); a dopamine blocker, such as haloperidol (HALDOL®); a β-blocker, such as propranolol (INDERAL®, INDERAL-LA®); a carbonic anhydrase inhibitor, such as acetalzolamide (DIAMOX®) or methazolamide (NEPTAZANE®); a narcotic agent, such as codeine (TYLENOL # 3®); a GABAergic agent, such as gabapentin (NEURONTIN®); or an alpha antagonist, such as clonidine (CATAPRESS®).

In certain embodiments, the formulation further comprises a stool softener selected from: bran or psyllium (*e.g.*, Metamucil, Fiberall), methylcellulose (*e.g.*, Citrucel), polycarbophil, docusate (*e.g.*, Colace, Surfak), docusate sodium and casanthranol combination (*e.g.*, Peri-Colace, Diocto C, Silace-C), magnesium hydroxide (*e.g.*, Phillips' Milk of Magnesia), magnesium citrate, sorbitol, polyethylene glycol solution (*e.g.*, MiraLax),

lactulose (*e.g.*, Cephulac, Cholac, Constilac), lubiprostone (*e.g.*, Amitiza) or other osmotic or stimulant laxatives (*e.g.*, Bisacodyl, Cascara, Castor oil, Senna, Tegaserod / Zelnorm), and natural stool softeners.

Alternatively, the stool softener(s) may be separately administered. For example, the stool softener(s) may be administered at a time when the effective compositions of first IR portion, the second substantially zero order release portion, or the substantially ascending release portion (such as the second IR portion) are being released.

Particular such embodiments provide a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa or the precursor in the patient in less than about 2 hours of administration to the patient; and, (2) a second substantially zero order release portion comprising levodopa or the precursor, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa or the precursor in the patient; wherein at least the first IR portion further comprises a decarboxylase enzyme inhibitor, and the ratio of the inhibitor to levodopa or the precursor in at least the first IR portion is greater than 1:4.

In certain embodiments, the ratio of the decarboxylase inhibitor to levodopa or its precursor in the first IR portion is about 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, or greater. The ratio may be different in different portions or sub-portions. For example, in the second sustained release portion, two or more sub-portions may be present, each having a different inhibitor / levodopa ratio. In certain embodiments, the ratio for the sub-portions to be released first (earlier) may be higher than that for the sub-portions to be released last (later).

In addition, the carbidopa and levodopa compositions may be released at different rates from different portions or sub-portions. For example, although the carbidopa / levodopa ratio may be consistently 1:4 in all subportions of the second substantially zero order release portion, the earlier sub-portions may release carbidopa faster, such that the release carbidopa / levodopa ratio is more than 1:4. Thus "release ratio" is defined as the ratio of two substances (*e.g.*, carbidopa and levodopa) released at a given time point.

In certain embodiments, the pharmaceutical composition further comprises: (3) a substantially ascending release portion (such as the second IR portion) comprising levodopa or the precursor, formulated to effect a rapid drop of levodopa concentration in the patient to

below the therapeutically effective concentration at the end of the treatment period.

In a related embodiment, the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa or the precursor in the patient within about 2 hours of administration to the patient; (2) a second substantially zero order release portion comprising levodopa or the precursor, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa or the precursor in the patient; and (3) a substantially ascending release portion comprising levodopa or the precursor, formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

In certain embodiments, the levodopa concentration in the patient drops below the therapeutically effective concentration at the end of the treatment period within about 2 hours, *e.g.*, within about 45 minutes, 1 hour, 1.5 hours, or 2 hours after the start of the substantially ascending release portion.

In certain embodiments, the levodopa precursor may be a methyl, ethyl, or propyl ester of levodopa, or a combination thereof. In certain embodiments, the levodopa precursor may be (−)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid, 3-hydroxy-L-tyrosine ethyl ester, phenylglycine, or a mixture thereof.

In certain embodiments, the ratio of the decarboxylase inhibitor to levodopa or the precursor in the first IR portion is about 1:3 or greater.

In certain embodiments, one or more of the various portions may comprise one or more additional drugs, such as the ones listed above.

In certain embodiments, the release ratio of the decarboxylase inhibitor to levodopa and/or its precursor varies between the start and the end of dispensing the second substantially zero order release portion.

In certain embodiments, the ratio changes substantially continuously over the release period of the second substantially zero order release portion.

In certain embodiments, the ratio is substantially constant during all or a part of the release period of the second substantially zero order release portion.

In certain embodiments, the substantially ascending release portion (such as the

second IR portion) comprises a decarboxylase enzyme inhibitor.

In certain such embodiments, the ratio of the inhibitor to levodopa and/or the precursor in the second IR portion is less than 1:4, such as 1:6, 1:8, 1:10, 1:15, 1:20, or less.

In certain embodiments, decarboxylase enzyme inhibitor is carbidopa, a carbidopa prodrug, benserazide, methylphenidate, or a combination thereof.

Unlike levodopa, carbidopa and benserazide are not pharmacologically / pharmaco-dynamically active, and they both have excellent toxicological profiles.

In certain embodiments, the total dose of the decarboxylase enzyme inhibitor per day per human patient is in the range of about 75 – 600 mg, or in the range of about 100 – 500 mg, or in the range of about 100 – 400 mg.

In certain embodiments, the total dose of levodopa and/or metabolic precursor thereof per day per human patient is between about 50 mg and about 300 mg.

In certain embodiments, at least one of the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) further comprises at least one dopamine transport inhibitor, preferably in sufficient amount to decrease dopamine elimination.

In certain embodiments, the dopamine transport inhibitor is methylphenidate.

In certain embodiments, the dopamine transport inhibitor is present in an amount of about 3 mg to about 60 mg.

In certain embodiments, the dopamine transport inhibitor is released starting after a delay of about 2 hours to about 7 hours.

In certain embodiments, the dopamine transport inhibitor is released over a period of time of about 1 hour to about 6 hours.

In certain embodiments, the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) (if present), are formulated to provide a sustained dose over at least 4 hours, 6 hours, 7 hours, 8 hours, 12 hours, 16 hours, 20 hours, or 24 hours when administered to the patient.

In certain embodiments, the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) (if present), are formulated into a stack of compressed inserts encased inside a shell or coating, each portion having an independent dissolution profile, wherein drug is released only from an exposed surface at a predetermined face of the stack, *e.g.*, through an opening at one end of the shell (*e.g.*, the multilayered tablet).

In certain embodiments, some or all of the beads are coated by a dispersion-promoting coating, *e.g.*, exterior to a bioadhesive coating.

In certain embodiments, the beads are less than about 1 mm in diameter.

In certain embodiments, the beads are dispersed in a matrix that disintegrates in less than about 5 minutes, 4 min., 3 min., 2 min., or less than 1 min.

In certain embodiments, the beads are dispersed in an eroding tablet that gradually erodes over the treatment period.

In certain embodiments, the tablet is at least partially coated by a bioadhesive material and/or an immediate release portion.

In certain embodiments, the bioadhesive material, if present, is exposed upon dissolution of the immediate release portion.

In certain embodiments, the shell is fully or partially coated by a bioadhesive polymeric material.

In certain embodiments, the composition contains no bioadhesive material, although other inert compositions, such as those found in the insert backing layer(s) of certain tablets (*e.g.*, ethylcellulose (ETHOCEL™ Std. 10 or 20 Premium), methylcellulose (METHOCEL™ K100M), magnesium stearate, *etc.*) may be present, *e.g.*, in place of the bioadhesive materials decribed for a particular embodiment. Such inert compositions may be chosen to be substantially insoluble in water, substantially impermeable to passage of biological fluids and/or the active agent(s), non-porous, and/or substantially non-swelling (*e.g.*, the volume of the material increases by less than 25%, preferably less than 10%, when placed in a biological medium).

In certain embodiments, the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) (if present), are each formulated as a one or more, preferably a plurality of, individual beads, each of the portions having an independent dissolution profile (*e.g.*, the multiparticulate capsule).

In certain embodiments, the ratio of beads corresponding to the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) (if present), are customized for the patient to provide a predetermined release profile, *e.g.*, to provide a predetermined duration of release, a predetermined rate of reaching a therapeutic plasma concentration of the drug or prodrug, or a predetermined maximum release rate (*e.g.*, customized for the size, sensitivity, or clearance

rate of the particular patient), *etc.* For example, using more of the first IR portion may increase the rate at which a therapeutic plasma concentration is reached, using more of the second substantially zero order release portion may increase the maximum release rate and the sustained plasma concentration of the drug or prodrug, and using a different second substantially zero order release portion (or an additional sustained release portion) having additional reserves of drug or additional coatings to delay release can extend the duration of the sustained release phase.

In certain embodiments, some or all of the beads are fully or partially coated by a bioadhesive polymeric material. For example, the beads in the first IR portion may not be coated, but the beads of the second (if present) and third portions (if present), may be so coated to assist delivery of drug over an extended period of time.

In certain embodiments, at least the substantially zero-order release rate second portion is coated or partially covered by a bioadhesive polymeric material.

In certain embodiments, the bioadhesive polymeric material is selected from polyamides, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, polyvinylpyrrolidone, polyglycolides, polyurethanes, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), polyanhydrides, polyorthoesters, poly(fumaric) anhydride), (need to make sure these are fixed throughout specification), blends, and copolymers thereof.

In certain embodiments, the bioadhesive polymeric material is poly(fumaric-co-sebacic) anhydride.

In certain embodiments, the bioadhesive polymeric material comprises a catechol moiety. For example, the bioadhesive polymeric material may comprise a mixture of a polymeric material and a compound comprising a catechol moiety selected from L-dopa, D-dopa, dopamine, or carbidopa. In addition, the bioadhesive polymeric material may be selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends and copolymers thereof.

In certain embodiments, the bioadhesive polymeric material is covalently functionalized with a catechol moiety, such as one derived from L-dopa, D-dopa, dopamine,

or carbidopa.

In certain embodiments, the pharmaceutical composition is formulated for oral administration, or for parental administration.

In certain embodiments, the pharmaceutical composition is suitable for human administration, or for veterinary treatment of a non-human mammal.

In certain embodiments, the pharmaceutical composition is provided in solid forms (*e.g.*, powders, beads, *etc.*). In other embodiments, certain portions or the whole pharmaceutical composition are in liquid forms. For example, the IR portion may be in the form of a liquid, while the CR (second) portion or sub-portions may be suspended as tiny particles or beads in the liquid IR. Alternatively, an inert pharmaceutically acceptable material, carrier, or excipient may be liquid, while both the IR and the CR may be suspended as tiny particles or beads in the liquid.

In certain embodiments, at least one adverse side effect (*e.g.*, the on-off effect or the the wearing off effect, *etc.*) associated with the treatment of a patient suffering from Parkinson's disease and/or another movement disorder is reduced or eliminated.

In certain embodiments, the subject pharmaceutical composition provides a substantially reduced degree of fluctuation in the plasma levels of the effective ingredients (*e.g.,* levodopa or carbidopa) compared to an immediate release pharmaceutical composition of the same dose administered three times daily.

Another aspect of the invention provides a method of making a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising combining the first IR portion, the second substantially zero order release portion, the substantially elevating release portion (if present), and the substantially ascending release portion (such as the second IR portion) (if present), of any of the subject pharmaceutical composition into a single dosage form.

Another aspect of the invention provides a method of treating a patient suffering from Parkinson's disease and/or another movement disorder, comprising administering to the patient any of the subject pharmaceutical compositions discussed herein.

In certain embodiments, the method comprises first administering to the patient the subject pharmaceutical composition with the first IR portion and the second zero-order release portion, followed by administering the substantially ascending release portion when the previously administered pharmaceutical composition is or is about to be completed in the patient.

Another aspect of the invention provides a packaged pharmaceutical preparation comprising the subject pharmaceutical composition, in an amount sufficient to treat a patient suffering from Parkinson's disease or another movement disorder, a pharmaceutically acceptable carrier, and a label or instructions (written and/or pictorial) for the use of the formulation for treating Parkinson's disease or another movement disorder, wherein the pharmaceutical composition is formulated to provide a sustained and/or increasing dose over at least about 6, 7, 8, 10, 12, 14, 16, 18, 20, or more hours when administered to the patient.

Another aspect of the invention provides a pharmaceutical preparation comprising the subject pharmaceutical composition, provided in the form of a transdermal patch and formulated for sustained release of the pharmaceutical composition in order to administer an amount sufficient to treat a patient suffering from Parkinson's disease and/or another movement disorder, wherein the pharmaceutical composition is formulated to provide a sustained substantial zero-order release over at least about 6, 7, 8, 9, 10, 12, 14, 16, 18, 20 or more hours when the patch is applied to the patient.

Another aspect of the invention provides a single dosage formulation for treatment of a movement disorder comprising levodopa or a metabolic precursor thereof, wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa or precursor thereof over a period of at least about 7, 8, 9, 10, 12, 14, 16, 18, 20 or more hours.

In certain embodiments, the single dosage formulation further comprises a decarboxylase enzyme inhibitor.

In certain embodiments, the single dosage formulation includes a first immediate-release (IR) portion to attain a therapeutically effective concentration of the levodopa or precursor with about 2 hours (*e.g.*, about 1.5 hrs, 1 hour, 45 min., 30 min., 20 min., 15 min., 10 min., 5 min., 2 min., 1 min., *etc.*) of administration to a patient. In certain embodiments, the single dosage formulation may further comprises: (1) a sustained zero-order release portion to maintain the therapeutically effective concentration of levodopa over a first period of hours; and, (2) a substantially ascending-release portion to maintain the therapeutically effective concentration of levodopa at the end of the sustained zero-order release portion; wherein the single dosage formulation, upon administration to the patient, produces a therapeutically effective concentration of the levodopa or precursor with about 2 hours (*e.g.*, less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1

min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administration to a patient.

In certain embodiments, the ascending release portion provides for a rate of decrease of levodopa in the patient from a therapeutically effective concentration to a sub-therapeutically effective concentration (*e.g.*, < 75%, 50%, 25% or less) in a second period of time less than about 2 hours, *e.g.*, within about 45 minutes, 1 hour, 1.5 hours, or 2 hours, *e.g.*, to reduce sleep side effects.

In certain embodiments, the ratio of the inhibitor to levodopa or the precursor in at least the first IR portion is greater than 1:4.

In certain embodiments, the decarboxylase enzyme inhibitor is present in only the first IR portion and the sustained zero-order release portion.

In certain embodiments, the decarboxylase enzyme inhibitor is present in all the portions, wherein the ratio of decarboxylase enzyme inhibitor to levodopa is different amongst different portions, *e.g.*, the ratio is higher in earlier-released portions than in later-released portions.

In certain embodiments, the sustained zero-order release portion comprises two or more sub-portions differing in the ratio of decarboxylase enzyme inhibitor to levodopa, *e.g.*, the ratio is higher in earlier-released portions than in later-released portions.

In certain embodiments, at least one of the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion further comprise at least one dopamine transport inhibitor, preferably in sufficient amount to decrease dopamine elimination.

In certain embodiments, the second substantially zero order release portion, and/or the substantially ascending release portion further comprise a bioadhesive polymeric material.

In certain embodiments, the the bioadhesive polymeric material comprises an additive that stabilizes the polymeric material from erosion, dissolution or both, wherein at least 50% by weight of a 1 mm thick film of the bioadhesive material remains after 12 hours in a buffered pH 4.5 dissolution bath.

In certain embodiments, the bioadhesive polymeric material comprises an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

Another aspect of the invention provides a single dosage formulation for treatment (*e.g.*, once-a-day) of a movement disorder comprising levodopa or a metabolic precursor thereof, and a decarboxylase enzyme inhibitor, wherein the single dosage formulation, upon

administration to the patient, produces a therapeutically effective concentration of the levodopa or precursor with about 2 hours (*e.g.*, in less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administration to a patient, the therapeutically effective concentration being maintained for a period of hours, then at the end of the dosing decreases to a sub-therapeutically effective concentration to, for example, reduce sleep side effects, in a period of time less than about 2 hours, *e.g.*, within about 45 minutes, 1 hour, 1.5 hours, or 2 hours.

Another aspect of the invention provides a therapeutic composition as described above, except that the dosage form is coated by a layer of delayed-release coating, such that the first IR portion will not start to be released until after a pre-determined period of time, such as the normal 6-10 hours of sleep time. According to this embodiment, a dose taken by the patient at night, for example, just before sleep, would start to be released and thus become effective just before or around the time the patient wakes up in the morning. This would allow the patient to have an effective plasma concentration of levodopa or precursor thereof upon waking in the morning, and the patient can immediately participate in normal daily activities without delay.

An additional advantage of the subject formulation relates to tolerance. Specifically, with enteral infusion, patients generally develop tolerance after prolonged period of treatment. However, the subject formulation has the added benefit of having a “break” during the night, so tolerance is generally not developed.

In a related aspect, the invention provides a general method of delivering a pharmaceutical composition, comprising administering to an individual the pharmaceutical composition coated by a delayed release coating, such that the release of the effective components of the pharmaceutical composition is delayed by a predetermined period of time, *e.g.*, at least about 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, or more.

In a related aspect, the invention provide a pharmaceutical composition coated by a delayed release coating, such that upon administering the pharmaceutical composition to an individual, the release of the effective components of the pharmaceutical composition is delayed by a predetermined period of time, *e.g.*, at least about 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, or more.

In certain embodiments, the pharmaceutical composition is administered at night, such that the delayed release starts the next morning.

In certain embodiments, the pharmaceutical composition with the delayed release coating is administered with the same pharmaceutical composition without the delayed release coating, such that the individual needs only take medicine once rather than twice (or multiple times) a day.

Another aspect of the invention provides a packaged pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first pharmaceutical composition comprising the subject pharmaceutical composition for day time administration (*e.g.,* need not have sleep-inducing agent); (2) a second pharmaceutical composition comprising the subject pharmaceutical composition for night time administration (*e.g.,* comprising sleep-inducing agent).

In certain embodiments, the first and/or the second pharmaceutical composition is packaged separately as individual doses.

In certain embodiments, the the package comprises at least one dose each of the first and the second pharmaceutical compositions.

In certain embodiments, the first and the second pharmaceutical compositions are distinctively marked by color, shape, and/or size.

In certain embodiments, the packaged pharmaceutical composition further comprises an instruction that instructs a patient to take the first pharmaceutical composition as a day dose, and to take the second pharmaceutical composition as a night dose.

In certain embodiments, the package comprises sufficient doses for treating a patient over a week, 2 weeks, a month, 3 months, 6 month or more.

Another aspect of the invention provides drug delivery devices, such as those described herein below (*e.g.*, those in Figures 1-14 and 18-42, and those described in the Examples. Effective compositions (drugs and/or prodrugs, *etc.*) in these devices may be formulated to achieve any desired release profiles. In the case of levodopa / carbidopa delivery, for example, these devices may be used to achieve the subject drug release profiles, such as those depicted in Figures 15 and 16. Typically, it is desired that the patient's plasma levels of levodopa are within a therapeutic window, *e.g.*, between about 680 and 3400 ng/mL, during periods of activity, *e.g.*, during most or all waking hours. Preferably, administration of a composition of the invention does not provide a plasma level of levodopa above 3400 ng/mL at any time during the course of administration.

Thus, one aspect of the invention provides a multiparticulate pharmaceutical composition, comprising: (1) a plurality of pellets, each said pellets comprising a core

comprising one or more effective ingredients; and (2) a matrix material; wherein the pellets are dispersed in the matrix material, and are released upon dissolution of the matrix material.

In certain embodiments, the matrix material disintegrates within about 5 minutes, 4 min., 3 min., 2 min., or less than 1 minute in an aqueous solution.

In certain embodiments, the aqueous solution is gastric acid.

In certain embodiments, the matrix material comprises a cushioning material.

In certain embodiments, the pharmaceutical composition is an eroding tablet and the matrix material gradually erodes over a predetermined period of time.

In certain embodiments, the eroding tablet is at least partially coated by a support material or a bioadhesive material.

In certain embodiments, the plurality of pellets comprises two or more different types of pellets.

In certain embodiments, a first type of pellets further comprises one or more coatings around the core of each pellet.

In certain embodiments, the coatings comprise a bioadhesive polymer, a composition for controlled release, and a dispersion-promoting composition.

In certain embodiments, the coatings comprise a bioadhesive polymer, a composition for controlled release, a composition for delayed release, a dispersion-promoting composition, and/or a functional or non-functional polymer.

In certain embodiments, the different coatings, if present, are in two or more discrete layers.

In certain embodiments, at least two different coatings, *e.g.*, a bioadhesive polymeric material and a controlled-release composition, are combined in the same coating layer.

In certain embodiments, the layers comprise a controlled-release layer disposed around the core, a bioadhesive polymeric material layer disposed around the controlled-release layer, and a dispersion-promoting layer disposed around the bioadhesive polymeric material layer.

In certain embodiments, the effective ingredients comprise about 50-80% (v/v) of the coated pellets.

In certain embodiments, the effective ingredients are at least about 60% (v/v) of the coated pellets, and the effective ingredients are cohesive, plastic, and engage in hydrogen bonding.

In certain embodiments, the pellets are no more than 3 mm, 2 mm, 1 mm, 0.8 mm, 0.7

mm, 0.5 mm, 0.3 mm, or 0.1 mm in size.

In certain embodiments, the pellets are substantially homogeneous in size and/or shape.

In certain embodiments, the core is substantially free of microcrystalline cellulose.

In certain embodiments, the effective ingredient is one or more of: metformin, acyclovir, ranitidine, riboflavin, chlorthiazide, gabapentin, losartin potassium, ganciclovir, cimetidine, minocycline, fexofenadine, bupropion, orlistat, captopril, diphenhydramine, tripelennamine, chlorpheniramine maleate, promethazine, omeprazole, prostaglandin, carbenoxolane, sucralphate, isosorbide, quinidine, enalapril, nifedipine, verapamil, diltiazem, nadolol, timolol, pindolol, salbutamol, terbutaline, carbuterol, broxaterol, aminophylline, cyclizine, cinnarizine, domperidone, alizapride, vincristine, megestrol acetate, daunorubicin, actinomycine, adriamycin, etoposide, 5-fluorouracil, indomethacin, sulindac, piroxicam, ibuprofen, naproxen, ketoprofen, temazepam, lorazepam, flunitrazepam, amantadine, ampicillin, amoxicillin, erythromycin, tetracyclines, cyanocobalamin, amino acids, iron or calcium salts of essential trace elements, or pharmacologically acceptable salts thereof.

Another aspect of the invention provides method to formulate a pharmaceutical composition, comprising: (1) blending the pharmaceutical composition to form a dry mix; (2) granulating the dry mix under low shear condition with a granulation fluid to form a wet granulation; (3) extruding the wet granulation through a screen-type extruder to form extrudate; (4) spheronizing the extrudate to form spheronized pellets; and (5) drying the pellets.

In certain embodiments, the pharmaceutical composition comprises two or more effective ingredients.

Another aspect of the invention provides method to formulate a pharmaceutical composition, comprising: (1) blending the pharmaceutical composition to form a dry mix; (2) granulating the dry mix under

In certain embodiments, the eroding tablet is at least partially coated by a support material or a bioadhesive material.

Another aspect of the invention provides a pharmaceutical composition formulated by any of the subject methods.

Another aspect of the invention provides a method to formulate a pharmaceutical composition, comprising: (1) blending the pharmaceutical composition to form a dry mix; (2) granulating the dry mix under low shear condition with a granulation fluid to form a wet

granulation; (3) drying the wet granulation to form dried granulation; (4) grinding the dried granulation, and sieving through a screen of predetermined size to form sieved granules; (5) blending in a lubricant to the sieved granules to form a uniformly lubricated dry mix.

In certain embodiments, the the pharmaceutical composition comprises two or more effective ingredients.

In certain embodiments, the the effective ingredients comprise levodopa and/or a metabolic precursor thereof, and a decarboxylase enzyme inhibitor.

In certain embodiments, the pharmaceutical composition comprises a bioadhesive polymeric material and/or a pharmaceutically acceptable excipient.

In certain embodiments, the pharmaceutical composition is substantially free of microcrystalline cellulose.

In certain embodiments, in step (1), the pharmaceutical composition is substantially free of lubricants.

In certain embodiments, the granulation fluid is purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone.

In certain embodiments, the method further comprises: passing the lubricated dry mix through a second screen.

In certain embodiments, the method further comprises: compressing the lubricated dry mix into a tablet.

In certain embodiments, the method further comprises: film-coating the tablet with one or more coating compositions.

In certain embodiments, the coating compositions comprise a bioadhesive polymeric material, a composition for controlled-release, a composition for delayed-release, a dispersion-promoting composition, and/or a functional or non-functional polymer.

In certain embodiments, the different coating compositions, if present, are in discrete layers.

In certain embodiments, at least two different coating compositions are mixed in the same coating layer.

Another aspect of the invention provides a pharmaceutical composition formulated with the subject methods.

Another aspect of the invention provides a multiparticulate pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising: (a) a plurality of pellets comprising levodopa or a metabolic precursor thereof (levodopa pellets), and (b) a plurality of pellets comprising carbidopa or a prodrug thereof (carbidopa pellets), wherein said first IR portion is formulated to provide a therapeutically effective concentration of levodopa in the patient within about 30 minutes of administration to the patient, and (2) a second portion comprising a plurality of pellets (levodopa-carbidopa pellets), each comprising: (a) a first core comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof); and (b) a bioadhesive polymeric material coating the first core, wherein said second portion is formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

In certain embodiments, the w/w ratio of carbidopa: levodopa is about 1:4 in the first and second portions.

In certain embodiments, the second portion comprises about 80-90% of the levodopa in the pharmaceutical composition.

In certain embodiments, the pharmaceutical composition further comprises: (3) a third portion comprising a plurality of pellets (levodopa-bioadhesive pellets), each comprising: (a) a second core comprising levodopa (or a metabolic precursor thereof); and, (b) a bioadhesive polymeric material coating the second core, wherein the second and third portions are formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

In certain embodiments, the second and third portions comprise about 80-90% of the levodopa in the pharmaceutical composition.

In certain embodiments, the second portion comprises about 60-70% of the levodopa in the pharmaceutical composition.

In certain embodiments, the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets are all disposed in a capsule.

In certain embodiments, the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets are all dispersed in a matrix material that disintegrates within about 5 minutes in an aqueous solution.

In certain embodiments, the matrix material comprises a cushioning material, *e.g.,* for absorbing shocks and/or reducing frictions on the surface of the coated pellets.

In certain embodiments, the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets are all dispersed in a matrix of an eroding tablet that gradually erodes over a predetermined period of time.

In certain embodiments, the eroding tablet is at least partially coated by a support material or a bioadhesive material.

In certain embodiments, the bioadhesive polymeric material coating the first and the second cores further comprises a dispersion-promoting agent, such as hydroxypropylcellulose.

In certain embodiments, the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets (if present) are no more than about 2 mm, 1 mm, 0.8 mm, 0.7 mm, 0.5 mm, 0.3 mm, or 0.1 mm in size.

In certain embodiments, the pellets are substantially homogeneous in size and/or shape.

In certain embodiments, the pharmaceutical composition is substantially free of microcrystalline cellulose.

In certain embodiments, the bioadhesive material comprises an additive that stabilizes the material from erosion, dissolution or both, wherein at least 50% by weight of a 1 mm thick film of the bioadhesive material remains after 12 hours in a buffered pH 4.5 dissolution bath.

In certain embodiments, the bioadhesive material comprises an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

Another aspect of the invention provides a multilayer tablet pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first controlled-release (CR) layer comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), wherein the w/w ratio of carbidopa : levodopa is about 1:4 in the CR layer; (2) a second, bioadhesive layer covering at least a portion of the first CR layer; wherein the tablet is formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

In certain embodiments, the multilayer tablet pharmaceutical composition further

comprises: (3) a third, immediate-release (IR) layer comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), said third layer covering at least a portion of the first CR layer and/or the second bioadhesive layer, wherein the w/w ratio of carbidopa : levodopa is about 1:4 in the third IR layer.

In certain embodiments, the CR layer comprises about 75-85%, or about 80% of the total levodopa in the composition.

In certain embodiments, the subject multilayer tablet pharmaceutical composition further comprises: (4) a fourth, pre-compressed immediate-release (IR) portion comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), wherein said fourth portion is disposed within the CR layer, and wherein the w/w ratio of carbidopa : levodopa is about 1:4 in the fourth portion.

In certain embodiments, the fourth portion comprises about 15-25% of the total levodopa in the composition, and the CR layer comprises about 50-70% of the total levodopa in the composition.

Another aspect of the invention provides a pharmaceutical composition comprising: a decarboxylase enzyme inhibitor formulated to provide an effective plasma concentration of the decarboxylase enzyme inhibitor over a predetermined extended period of time after the administration of the pharmaceutical composition to the patient. Optionally, the pharmaceutical composition further comprises: (1) one or more bioadhesive layers, (2) one or more bioadhesive compositions, *e.g.*, incorporated in the pharmaceutical composition, or (3) one or more bioadhesive compositions incorporated, *e.g.*, as layers, in the pharmaceutical composition, for example, as a multilayer tablet. These subject pharmaceutical compositions may be useful for preferentially targeting the release of the decarboxylase enzyme inhibitor at a target absorption site. The formulation may be in many different forms, such as a matrix tablet, a bilayer tablet, a trilayer tablet, or a multiparticulate capsule, *etc.*

In certain embodiments, the pharmaceutical composition is substantially free of levodopa.

In certain embodiments, the pharmaceutical composition is substantially free of immediate release formulation of decarboxylase enzyme inhibitors. For example, in certain embodiments, less than 50%, 25%, 15%, or even 10% of the decarboxylase enzyme inhibitors in the pharmaceutical composition is released within the first hour or first 2 hours after administration to the patient. In certain embodiments, less than 50%, less than 25%, less than 15% or even less than 10% of the decarboxylase inhibitor in the formulation is released

within the first hour, or even the first two hours, after release of the decarboxylase inhibitor commences.

In certain embodiments, the decarboxylase enzyme inhibitor is formulated to provide a constant effective plasma concentration starting at least about 4 hours after administration to the patient.

In certain embodiments, the predetermined extended period of time is about 7-14 hours, 8-14 hours, or about 9-13 hours, or about 10-12 hours, or about 11 hours.

In certain embodiments, the decarboxylase enzyme inhibitor is released at a substantially constant rate over the predetermined extended period of time.

In certain embodiments, the decarboxylase enzyme inhibitor is formulated in a partially exposed core between two bioadhesive layers.

In certain embodiments, the target absorption site is proximal to the small intestine, such as proximal small intestine.

In certain embodiments, the composition further comprises a sleep-inducing agent, such as those described herein.

In certain embodiments, the composition further comprises one or more of: a dopaminergic and anti-cholinergic agent selected from: amantadine; an anti-cholinergic agent selected from: trihexyphenidyl, benztropine, ethoproprazine, or procyclidine; a dopamine agonist selected from: apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, or ropinirole; a MAO-B (monoamine oxidase B) inhibitor selected from: selegiline or deprenyl; a COMT inhibitor selected from: CGP-28014, entacapone, or tolcapone; a muscle relaxant, such as baclofen; a sedative Clonazepam; an anticonvulsant agent carbamazepine; a dopamine reuptake inhibitor tetrabenazine; a dopamine blocker haloperidol; a β-blocker selected from: propranolol; a carbonic anhydrase inhibitor selected from: acetalzolamide or methazolamide; a narcotic agent codeine; a GABAergic agent gabapentin; an alpha antagonist clonidine; a stool softener selected from: bran or psyllium, methylcellulose, polycarbophil, docusate, docusate sodium and casanthranol combination, magnesium hydroxide, magnesium citrate, sorbitol, polyethylene glycol solution, lactulose, lubiprostone or other osmotic or stimulant laxatives, and a natural stool softener; or a dopamine transport inhibitor.

In certain embodiments, the decarboxylase enzyme inhibitor is carbidopa, a carbidopa prodrug, benserazide, methylphenidate, or a combination thereof.

In certain embodiments, the total dose of the decarboxylase enzyme inhibitor is about

25 – 300 mg, about 50 – 200 mg, or about 100 mg.

In certain embodiments, the one or more bioadhesive layers include bioadhesive materials selected from chitosan, hyaluronic acid, hyaluran, thiomers, poly(methylvinylether-co-malic anhydride), polyamides, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, carbopols, carbomers, polyvinylpyrrolidone, polyglycolides, polyurethanes, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends and copolymers thereof.

In certain embodiments, the one or more bioadhesive layers include poly(fumaric-co-sebacic) anhydride.

In certain embodiments, the one or more bioadhesive layers comprise bioadhesive materials having a catechol moiety.

In certain embodiments, the bioadhesive materials comprise a mixture of a material and a compound comprising a catechol moiety selected from L-Dopa, D-dopa, dopamine, or carbidopa.

In certain embodiments, the bioadhesive materials are selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends, and/or copolymers thereof.

In certain embodiments, the one or more bioadhesive layers comprise bioadhesive material covalently functionalized with a catechol moiety.

In certain embodiments, the catechol moiety is derived from L-dopa, D-dopa, dopamine, or carbidopa.

In certain embodiments, the one or more bioadhesive layers comprises an additive that stabilizes the bioadhesive layers from erosion, dissolution or both, wherein at least 50% by weight of a 1 mm thick film of the bioadhesive layers remain after 12 hours in a buffered pH 4.5 dissolution bath.

In certain embodiments, the bioadhesive layers comprise an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

In certain embodiments, the composition is suitable for human treatment, or for

veterinary treatment of a non-human mammal.

Another aspect of the invention provides a method of making a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising combining the decarboxylase enzyme inhibitor with one or more bioadhesive layers of any of the subject pharmaceutical composition (*e.g.*, those comprising a decarboxylase enzyme inhibitor and formulated to provide an effective plasma concentration of the decayboxylase enzyme inhibitor over a predetermined extended period of time after the administration of the pharmaceutical composition to the patient, preferably lasting 6-12 hours, and optionally comprising one or more bioadhesive layers that may be useful for preferentially targeting the release of the decarboxylase enzyme inhibitor at a target absorption site) into a single dosage form.

Another aspect of the invention provides a method of treating a patient suffering from Parkinson's disease and/or another movement disorder, comprising administering to the patient any of a subject pharmaceutical composition (*e.g.*, those comprising a decarboxylase enzyme inhibitor and formulated to provide an effective plasma concentration of the decayboxylase enzyme inhibitor over a predetermined extended period of time after the administration of the pharmaceutical composition to the patient, preferably lasting 6-12 hours, and optionally comprising one or more bioadhesive layers that may be useful for preferentially targeting the release of the decarboxylase enzyme inhibitor at a target absorption site).

In certain embodiments, the pharmaceutical composition is administered before the patient goes to sleep.

In certain embodiments, the pharmaceutical composition is administered shortly before, with, or after the patient's last meal before going to sleep.

In certain embodiments, the method further comprises administering a second pharmaceutical composition comprising levodopa or metabolic precursor thereof 6-12 hours thereafter.

Another aspect of the invention provides a packaged pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first pharmaceutical composition comprising any of the subject pharmaceutical compositions (*e.g.*, those comprising a decarboxylase enzyme inhibitor and formulated to provide an effective plasma concentration of the decayboxylase enzyme inhibitor over a predetermined extended period of time after the administration of the

pharmaceutical composition to the patient, preferably lasting 6-12 hours, and optionally comprising one or more bioadhesive layers that may be useful for preferentially targeting the release of the decarboxylase enzyme inhibitor at a target absorption site); (2) a second pharmaceutical composition comprising levodopa or a metabolic precursor thereof.

In certain embodiments, the first and/or the second pharmaceutical compositions are packaged separately as individual doses.

In certain embodiments, the package comprises at least one dose each of the first and the second pharmaceutical compositions.

In certain embodiments, the first and the second pharmaceutical compositions are differentiated by color, shape, marking, imprinting, and/or size, *etc.*

In certain embodiments, the composition further comprises an instruction that instructs a patient to take the first pharmaceutical composition before sleep, and to take the second pharmaceutical composition after waking.

In certain embodiments, the package comprises sufficient doses for treating a patient over a week.

The invention also provides for bioadhesive granules. These granules can be used to fabricate new drug delivery or diagnostic systems with increased residence time at tissue surfaces, and consequently increase the bioavailability of a drug or a diagnostic agent. The bioadhesive granules of the invention can be prepared to be flowable and compressible, *e.g.*, suitable for use in drug manufacturing equipment and processes. For example, the bioadhesive granules of the invention can be compressed, *e.g.*, to manufacture a coating on a controlled release oral dosage formulation and/or form a matrix in an oral dosage formulation. For example, the granules may be compressed into a film, sheet, tablet, hollow, cylinder, ring, or rod, *etc.* The invention also provides for methods of manufacturing granules.

Thus in another aspect, the invention provides a method for the manufacture of granules comprising a bioadhesive polymer, comprising i) dissolving a bioadhesive polymer in a solvent to form a solution, ii) combining a second polymer with the solution, and, iii) evaporating solvent from said solution under conditions that result in the formation of granules.

In certain embodiments, the bioadhesive polymer comprises zein, shellac, thiomers, POLYOX™ polymers, CORPLEX™ polymers (Corium International, Redwood City, CA), GANTREZ® polymers (International Specialty Products, Wayne, NJ), gliadin, and/or

polycarbophils. In certain embodiments, the bioadhesive polymer is selected from SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ II, SPHEROMER™ III, and SPHEROMER™ IV polymers (such as those described herein).

In certain embodiments, the the second polymer is a hydrophobic polymer.

In certain embodiments, the second polymer is a hydrophilic polymer.

In certain embodiments, the second polymer is a non-bioadhesive polymer.

In another aspect, the invention provides bioadhesive granules comprising about 2% to about 20% of a bioadhesive polymer and about 80% to about 98% of a second polymer.

In certain embodiments, the bioadhesive polymer comprises zein, shellac, thiomers, POLYOX™ polymers, CORPLEX™ polymers, GANTREZ® polymers, gliadin, and/or polycarbophils. In certain embodiments, the bioadhesive polymer is selected from SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ II, SPHEROMER™ III, and SPHEROMER™ IV polymers (such as those described herein).

In certain embodiments, the second polymer is a non-bioadhesive polymer.

In certain embodiments, the second polymer is selected from methylcellulose (MC), carboxymethylcellulose (CMC), hydroxyethylcellulose (HEC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP), vinylpyrrolidone/vinyl acetate copolymer, polyethylene oxide (PEO), methacrylic acid copolymers, methacrylic ester copolymers, ammonioalkyl methacrylate copolymers, cellulose acetate, cellulose acetate butyrate, chitin, chitosan, and ethyl cellulose.

In certain embodiments, the granules can be compressed into a solid matrix.

In another aspect, the invention provides a bioadhesive polymer comprising a poly(ethylene-co-maleic anhydride) polymer backbone functionalized with residues of at least one compound comprising: (a) an aromatic moiety comprising two or more hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, and (b) a primary or secondary amino moiety. In certain embodiments, the cumulative amount of the compound, when not functionalized to a polymer backbone, that is converted to dopamine when infused into rat striatum is at least 65% less than for an equimolar amount of L-3,4-dihydroxyphenylalanine or wherein the blood-brain barrier is substantially impermeable to the compound, when not functionalized to a polymer backbone.

Embodiments described herein are contemplated to be combined with each other embodiments as appropriate. Embodiments described in detail under one aspect of the

invention may be equally applicable for the other aspects of the invention.

Brief Description of the Drawings:

Figure 1 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. Layers **11-13** represent the immediate-release composition layer (IR), the substantially zero-order release rate composition layer, and the optional ascending release (*e.g.*, second IR) layer, respectively. Layer **14** is an insoluble plug that seals off one end of the open-ended container / shell **15**. In this embodiment, Layers **11, 12,** (and optionally **13**) are exposed and released in sequential order.

Figure 2 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. Beads **21-23** represents the immediate-release composition portion (IR), the substantially zero-order release rate composition portion, and the optional ascending release portion (such as the second IR portion), respectively. The container / shell encompassing the beads may be made from any pharmaceutically acceptable material, such as gelatin, starch, HPMC (hydroxypropyl methylcellulose), pullulan, and fast dissolving capsules. The concentric rings on the beads represent different layers of coating, each of which layers may have different compositions and/or result in different release profiles.

Figure 3 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The three layers represents the immediate-release composition layer (IR) **31**, a bioadhesive layer (hatched lines) **32**, and the substantially zero-order release rate composition layer **33**. There may be one or more well-defined exit ports **34** on the bioadhesive layer to allow the inner contents to be released, or the bioadhesive layer **32** may be permeable to release of the encapsulated drug. The port size may increase in diameter over time, or when the dissolution progresses.

Figure 4 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. It is essentially identical to that depicted in Figure 3 (*e.g.*, having IR layer **41**, bioadhesive coating **42**, zero-order release core **43**, and exit port **44**), with an additional (optional) core **45** inside the substantially zero-order release rate composition layer **43**, which optional core **45** is the ascending release layer (such as the second IR layer).

Figure 5 is a schematic drawing (not to scale) illustrating a cross-sectional view of one

design of the subject delivery device. The three shown layers represent the immediate-release composition layer **(IR) 51**, and two substantially zero-order release rate composition layers **(CR1 52** and **CR2 53)**. There may be more than two such substantially zero-order release rate composition layers, differing by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson disease therapeutic composition). The inner trilayer core is coated with a semi-permeable coating **54a**, which is then coated over by a bioadhesive layer or patch (hatched lines) **54b**. The therapeutic compositions are successively released through an orifice **56** close to the IR composition (proximal end) **51**. Optionally, the distal end of the shell may comprise a plug **55** that can push the therapeutic compositions towards the orifice **56** at the proximal end. The push mechanism can be any suitable means, such as a water-absorbing gel that swells when in contact with aqueous solution, or a gas-generating unit, or a rigid plate / plunger that can be driven by a micromotor (optionally externally activated).

Figure 6 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The three shown cores represent the immediate-release composition core **(IR) 61**, and two substantially zero-order release rate composition cores **(CR1 62** and **CR2 63)**, each coated by its own bioadhesive layer (hatched lines **620** and **630**, respectively). There may be more than two such substantially zero-order release rate composition cores, differing by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson's disease therapeutic composition). All such cores are encased inside a shell **64** made from suitable materials such as gelatin.

Figure 7 is a schematic cross-section view (not to scale) of two embodiments of a portion of the dosage form (*e.g.*, the second zero-order release rate portion). In this specific example, the composition may be formed as a cylinder or a column, or have a trapezoid profile (right panel). The compositions (*e.g.*, levodopa **72** and carbidopa **71)** are released starting from the top face and progressing in the order shown by the arrow. The top (beginning) of the dosage form has a different carbidopa / levodopa ratio from the bottom (end) of the dosage form.

Figure 8 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The three shown layers represent the immediate-release composition core **(IR) 81**, one sub-portion of the substantially zero-order release rate composition **CR1 82**, and a second sub-portion of the substantially zero-order release rate composition **CR2 83**, in the form of beads with or without bioadhesive coating and/or

delayed release coating, and a bioadhesive composition layer **84** adjacent to the zero-order release rate composition **CR1 82**. There can be more than one sub-portions of the substantially zero-order release rate composition embedded within layer **82** (such as **CR3**, **CR4**, *etc.*, not shown). Each sub-portion may differ by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson's disease therapeutic composition). The different sub-portions may be coated with different delayed-release compositions (optionally with different thickness, *etc.*), and/or beads may adopt a patterned distribution within the **CR1** layer, such that the beads of the same sub-portion start to release therapeutic compositions at substantially the same time. Alternatively, beads of the same sub-portion may start to release therapeutic compositions at staggered time points to effect a specific release profile, such as an ascending release profile.

Figure 9 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The immediate-release composition layer **91** covers the bioadhesive composition layer **94**, which has a hollow core that may adopt any desired geometric shape (regular or irregular, symmetrical or asymmetrical). Once the IR layer **91** is dissolved, it exposes the peripheral ends of **CR1 93**. The bioadhesive layer **94** covers the inner contents, which are to be gradually released through the peripheral ends. In the shown embodiment, the center of the hollow core is occupied by a sub-portion of the zero-order release rate composition **CR2 92** (or the second IR release portion). The rest of the core is filled with other sub-portion(s) of the zero-order release rate composition **CR1 93**. The geometric shape allows gradually increasing (as shown) or decreasing (not shown) amounts of drugs to be released in unit time periods. Each sub-portion may differ by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson's disease therapeutic composition). The IR layer **91** can also be part of the **CR1 93** core, in form of a lip or lid (not shown).

Figure 10 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. In this shown embodiment, the device is shaped like a torus or donut with a central hole. The immediate-release composition layer **1001** covers the entire surface, or almost the entire surface of the device. Underneath the IR layer **1001** is the bioadhesive composition layer **1004**, which covers almost the entire surface except a portion of the inner surface of the donut hole. The inner core covered by the bioadhesive layer is one or more sub-portions of the zero-order release rate composition, for example, **CR1 1002** and/or **CR2 1003** as shown (or the second IR release portion). When the

IR layer is dissolved, the inner surface of the donut hole not covered by the bioadhesive layer is exposed, creating an exit hole to allow the CR sub-portions to be released from the inner core of the device. Although shown as regularly-shaped in the figure, the CR inner cores need not be of regular and/or symmetric shape. Neither does the two or more CR sub-portions need to be horizontally arranged to effect simultaneous release. A vertical arrangement of the CR sub-portions within the inner core may be used to effect sequential release of different CR sub-portions.

Figure 11 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The immediate-release composition **1101** covers the two ends of a rod-shaped device (although the IR can cover the entire surface of the device, not shown). Towards the more central parts of the rod are several sub-portions of the zero-order release rate composition **CR1 1102**, separated from one another by other sub-portions of the zero-order release rate composition **CR2 1103**. The release of each **CR2 1103** is delayed temporarily by a ring of bioadhesive composition **1104**, and by the adjacent layers of **CR1 1102**. Upon the fast release of IR **1101**, followed by sustained controlled release of **CR1 1102**, the rod may break into two or more smaller rods / parts due to the dissolution of **CR1 1102** sub-portions. Depending on the spacing between adjacent **CR2 1103** sub-portions, one or more **CR2 1103** sub-portions may start to release from one side, or both sides of the sub-portion.

Figure 12 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device – a bioadhesive buccal patch or buccal tablet attaching to a mucosa of the mouth **1201**. The immediate-release composition layer **1202** covers one sub-portion of the zero-order release rate composition **CR1 1203**, which covers another sub-portion of the zero-order release rate composition **CR2 1204** (or the second IR release portion). The whole device may be formulated as a multilaminate bioadhesive buccal patch or tablet attaching to a mucosa area of the mouth. Either or both CR layers may have their own bioadhesive layer or patch (not shown).

Figure 13 shows a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device – a dose sipping system. According to this embodiment, the therapeutic compositions are deposited in a straw plugged at one end by a porous plug **1303**. By dipping the plug end of the straw into a liquid (*e.g.*, a glass of water), and applying suction through the open end of the straw **1304**, the patient will receive the therapeutic composition in the solution taken through the straw. As shown, the immediate-

release composition **1301** forms a matrix that contains one or more sub-portions of the substantially zero-order release rate composition **CR1** and/or **CR2 1302**, in the form of beads with or without bioadhesive coating and/or delayed release coating. There can be more than one sub-portion of the substantially zero-order release rate composition embedded within matrix **1301** (such as **CR3**, **CR4**, *etc.*, not shown). The sub-portions may differ by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson's disease therapeutic composition). If the sub-portion(s) of the substantially zero-order release rate composition (*e.g.*, **CR1 1302**) are coated by bioadhesive layers, such sub-portions may adhere to the GI track and release their contents according to the designed release profile. Alternatively, the IR portion may also be formulated as beads embedded with the other CR beads within an inert matrix.

Figure 14 shows a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. According to this embodiment, the therapeutic compositions are encompassed within a shell with a cap **1404** and a body **1405**. The cap **1404** may be made of gelatin or other equivalent materials, while the body **1405** may be a bioadhesive layer itself, or a part of the gelatin body coated with a bioadhesive composition. Once the device is internalized by a patient and the gelatin cap **1404** is dissolved, the immediate-release composition **1401** will be exposed and quickly released. This in turn allows one or more sub-portions of the substantially zero-order release rate composition **CR1 1402** and/or **CR2 1403**, either in the form of beads embedded within an inert matrix (not shown), with or without bioadhesive coating and/or delayed release coating, or in the form of successive layers. Although the cross-section is shown as a rectangle, it can be in any suitable shape (such as oval), and need not be symmetrical or regularly shaped.

Figure 15 is a schematic drawing showing plasma concentration profiles of levodopa and carbidopa for an exemplary levodopa-carbidopa dosage formulation: Immediate Release – Controlled Release – Delayed/Extended Release profile.

Figure 16 is a schematic drawing showing plasma concentration profiles of levodopa and carbidopa for an exemplary levodopa-carbidopa dosage formulation: Immediate Release – Controlled Release - Ascending Release profile.

Figure 17 illustrates a blister packaging of an exemplary levodopa-carbidopa dosage formulation for day and night administration, *e.g.*, during a period of one week (other packages with different treatment cycles, such as monthly package with multiple such weekly packages, are also contemplated, but not shown). The dosage forms for day and night

administration can be differentiated by *e.g.*, color, and optionally by shape, marking, imprint, *etc.* The ratio of levodopa and carbidopa in the exemplary dosage formulations may be different for day and night administrations. In certain embodiments, the release rate of levodopa and carbidopa in the exemplary dosage formulations may be different for day and night administrations. In addition, the dosage form for night may comprise carbidopa extended release dosage (*e.g.*, substantially free of levodopa) followed by levodopa-carbidopa extended release dosage for morning delivery.

Figure 18 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 19 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 20 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 21 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 22 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 23 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 24 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 25 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 26 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 27 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 28 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 29 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 30 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 31 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 32 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 33 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 34 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 35 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 36 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 37 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 38 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 39 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 40 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 41 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 42 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 43 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for SINEMET® CR 50-200 tablets.

Figure 44 shows *in vitro* dissolution profiles of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg multilayer extended release tablets in 0.1 N HCl.

Figure 45 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for levodopa-carbidopa 200 mg/50 mg multilayer extended release tablets.

Figure 46 shows plasma concentration profiles of levodopa and carbidopa in fasted beagle dogs for levodopa-carbidopa 200 mg/50 mg multilayer extended release tablets.

Figure 47 shows plasma concentration profiles of levodopa in fed beagle dogs for

SINEMET® CR 50-200 Tablets and levodopa-carbidopa 200 mg/50 mg multiparticulate capsules.

Figure 48 shows plasma concentration profiles of carbidopa in fed beagle dogs for SINEMET® CR 50-200 Tablets and levodopa-carbidopa 200 mg/50 mg multiparticulate capsules.

Figure 49 shows *in vitro* dissolution profiles of levodopa and carbidopa for SINEMET® CR 50-200 Tablets in 0.1 N HCl.

Figure 50 provides an exemplary scheme or drug cycle regarding the release of different components of the subject single dosage formulation.

Figure 51 shows HPLC analysis of *in vitro* dissolution profiles of an exemplary carbidopa extended release tablet (Bioadhesive Carbidopa 100 mg Trilayer Extended Release Tablets) in 0.1 N HCl – pH 1.2 and in PBS – pH 4.5.

Figure 52 shows HPLC analysis of *in vitro* dissolution profiles of carbidopa extended release tablet (Bioadhesive Carbidopa 100 mg Trilayer Extended Release Tablets) in 0.1 N HCl – pH 1.2 and in PBS – pH 4.5.

Figure 53 shows plasma concentration profiles of cabidopa in fed beagle dogs for an exemplary carbidopa extended release tablet (bioadhesive carbidopa 100 mg Trilayer Extended Release Tablets).

Figure 54 shows plasma concentration profiles of levodopa and carbidopa in fed healthy young human volunteers for SINEMET® CR 50-200 Tablets.

Figure 55 shows plasma concentration profiles of levodopa and carbidopa in fed healthy young human volunteers for levodopa-carbidopa 200 mg/50 mg multilayer extended release tablets.

Figure 56 shows the particle size distribution of SPHEROMER™ III / ethylcellulose granules.

Figure 57 is a schematic drawing (not necessarily to scale) showing a possible drug release mechanism for the subject Levodopa-Carbidopa extended release (XL) tablets.

Figure 58 shows the result of a representative release profile study using the subject Levodopa-Carbidopa extended release (XL) tablets, which contain bioadhesive backing layers. The results for 6 individual tablets, as well as the average result, over a time period of 20 hours are shown.

Figure 59 shows the result of a representative release profile study using the subject Levodopa-Carbidopa extended release (XL) tablets, which backing layers do not contain

bioadhesive materials. The results for 6 individual tablets, as well as the average result, over a time period of 20 hours are shown.

Detailed Description of Invention:

I. *Overview*

In general, the present invention relates to the treatment of movement disorders, such as Parkinson's disease and other movement disorders. In certain embodiments, the invention relates to particular dosage forms that provide release profiles of the particular therapeutic compounds that are the most effective for the intended therapeutic use (*e.g.*, treatment of Parkinson's disease).

In one aspect, the present invention provides a dosage form and a method for administering a movement disorder pharmaceutical composition (*e.g.*, levodopa / carbidopa) in a once-a-day or more frequent regimen that ameliorates or overcomes symptoms of a movement disorder (*e.g.*, Parkinson's disease) in a patient.

In certain embodiments, the single dosage formulation of the subject invention comprises levodopa or a metabolic precursor thereof, and a decarboxylase enzyme inhibitor, wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa or precursor thereof over a period of at least about 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours or more. For example, In certain embodiments, the pharmaceutical composition of the single dosage formulation may comprise: (1) a first immediate-release (IR) portion that provides a therapeutically effective concentration of a drug in the patient with about 2 hours (*e.g.*, about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*) of administration to the patient; (2) a second substantially zero order release portion comprising the drug, formulated to release the drug at a substantially zero-order release rate over a predetermined sustained treatment period to maintain the therapeutically effective concentration of drug in the patient.

The subject dosage formulation is advantageous for reducing the "wearing off" and the "on off" issues. SINEMET® CR (DuPont Pharma), a controlled release dosage form was designed to provide slow and simultaneous release of levodopa and carbidopa (U.S. Pat. No. 4,900,755). In certain embodiments, the subject dosage formulations provide a longer period of levodopa release within the therapeutically effective concentration than SINEMET® does.

Certain embodiments of the invention overcome the gastric emptying problem, resulting in considerably less fluctuation in levodopa plasma levels, which in turn ameliorates the "on-off" problem.

Prolonged suppression of disease manifestations with many traditional dosage forms is constrained by the mechanism of absorption of levodopa from the gastrointestinal tract. Levodopa is absorbed by the active transport mechanism for amino acids, which is most active in the duodenum region of the small intestine. Sustained release is therefore limited by the transit time of the dosage form through the stomach and duodenum which, though highly variable from individual to individual and dependent upon nutritional state, typically takes only about 3 to 4 hours. Levodopa released after the 3-4 hour therapeutic window has passed is not bioavailable. SINEMET® CR carbidopa-levodopa controlled release tablets have about 75% of the bioavailability of SINEMET® carbidopa-levodopa conventional release tablets. *Physicians Desk Reference*, p. 979, (54th edition, Medical Economics Co., publisher, 2000). Mean time to peak concentration in healthy elderly subjects was found to be two hours for controlled release carbidopa-levodopa, and only 0.5 hours for the conventional form (*Physicians Desk Ref.*, 47th Ed., p. 976, 1993).

Certain delayed release dosage forms of the invention possess a coating that dissolves slowly in gastrointestinal fluid. Release of the active component is delayed until dissolution of the coating allows gastrointestinal fluid to contact a core of the dosage form containing the drug. In combination with such coatings, the invention further provides certain bioadhesive polymer materials that help retain the pharmaceutical composition, such as one including levodopa, in the stomach of the patient. Thus, the period of release of the composition is timed to capitalize on the window of bioavailability. In other words, certain dosage forms of the invention overcome the gastric emptying problem, resulting in considerably less fluctuation in levodopa plasma levels, which in turn alleviates the "on-off" problem. This is a significant advantage for delivering drugs like levodopa that have a short absorption window.

Another advantage of certain embodiments of the invention is that a high concentration of levodopa in a patient's system, such as a "long tail" of levodopa concentration drop resulting from large doses of controlled release of levodopa / carbidopa at the end of the regimen, may be avoided by using a substantially ascending release portion, such as a second IR portion, in the dosage form released at the end of the treatment window, *e.g.*, as the effects of carbidopa administration are waning, such that at the end of the therapeutic regimen (*e.g.*, at the end of the day), the plasma level of levodopa quickly drops

to below the effective level, so that the dosage form will not cause sleeping / resting problems for the patient.

Traditionally, in order to maintain a sufficient levodopa concentration at the end of the traditional release profile, a large dose of controlled release of levodopa / carbidopa has to be used at the end of the traditional regimen, resulting in a "long tail" of levodopa concentration drop long after the ending of the desired treatment period / cycle. This in turn causes sleeping / resting problems for the patient.

The subject release profile replaces the last segment of the traditional release profile with a last IR portion. According to the subject release profile, before the start of this last segment, effective concentration of carbidopa decreases / diminishes, allowing the body to metabolize levodopa faster and clearing it rapidly from the system. The presence of the last IR portion compensates for this more rapid processing, thus maintaining the effective levodopa concentration towards the end of the release profile. However, after the end of the desired treatment period / cycle (*e.g.,* end of the day), levodopa in the last IR portion is quickly consumed, leaving no undesirable long tail to interfere with the sleeping / resting of the patient.

In certain embodiments, the subject pharmaceutical compositions are formulated to deliver rapidly upon administration an immediate-release (IR) dose, followed by a sustained release dose to maintain the effective therapeutic concentration, *e.g.*, over at least 4 hours, and more preferably over at least 5, 8, 10, 12, 14, or even 16 hours after administration.

In certain embodiments, an immediate release is followed by a substantially zero-order release rate, which is optionally further followed by a substantially ascending rate of drug release, or additional immediate release. The substantially ascending rate of drug release compensates for the drop off in effective levodopa concentration in the patient's system when the second portion of substantial zero-order release reaches the end of its release profile (see Figure 15 below; compare the tail-down of the center curve, the corresponding rise of the right-most curve around the same time, and the relative stable plateau represented by the solid curve). For example, if the patient takes the medicine upon arising in the morning, a subsequent ascending release dose (such as the second IR portion) taken separately at mealtime (*e.g.*, dinner) would provide the patient with additional needed therapeutic agent, if necessary, without having to resort to a second full-dose of drug for the same treatment period (*e.g.*, day). The ascending portion (such as the second IR portion) may also be built into the single dosage treatment medicine (dosage form) such that the patient need only

administer treatment once a day in the morning.

Figure 15 shows an illustrative (non-limiting) release profile of the subject dosage form. According to Figure 15, the first IR portion (left-most sharp curve) allows a quick increase of levodopa concentration in a patient's system to within a therapeutically effective concentration range or window (the two dashed lines). This process should occur in less than about 2 hours (*e.g.*, about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hr, 1.5 hrs, 2 hrs, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administering the dosage form, depending on specific needs. As the concentration reaches its peak, or slightly before or after reaching the peak of the first IR portion release, the second sustained release portion begins to release (the middle dotted-curve in Figure 15), such that the total levodopa concentration is maintained within the therapeutic window. Certain fluctuation in concentration is tolerated, so long as the total concentration is not too high or too low to fall outside the effective therapeutic window.

The zero-order release from the second portion is expected to maintain the total concentration within the therapeutic window for several hours, such as about 4, 5, 6, 7, 8, 9, 10 or more hours, until the net release into the patient's system is less than the net uptake/metabolism by the system including metabolic processes and other degradation processes. At that point, the total concentration of levodopa may start to drop (the point where the middle dotted-curve touching the plateau region of the thick solid curve). In the absence of an optional ascending release portion (either built in the single dosage treatment regimen or taken separately), the effective concentration will assume a long-tailed drop. But with the optional ascending release portion (either built in the single dosage treatment regimen or taken separately), the release profile can be modified. According to this embodiment, the plateau region of the solid curve is extended to a total period of beyond about 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 20 hours or more. Again, some concentration fluctuation is tolerable during this extended plateau period, so long as it falls within the effective therapeutic window.

In an alternative embodiment, the substantially ascending release portion may comprise levodopa, formulated to elevate the substantially zero-order release rate to a higher level, beginning around a predetermined time point, such as within ½, 1, 1.5, or 2 hours of noon (*e.g.*, about 4-6 hours after administration to the patient).

At the end of the ascending release portion (such as the second IR portion), the (total)

concentration of levodopa may optionally be allowed to drop quickly, *e.g.*, within 30-120 minutes, such as within about 45 minutes, 1 hr, 1.5 hrs, or 2 hrs, to below a predetermined sub-therapeu-tically effective concentration through, for example, controlling the inhibitor / levodopa ratio.

As used herein, "sub-therapeutically effective concentration" refers to a value below the minimal effective concentration, such as less than about 75%, 50%, or about 25% of the minimal therapeutically effective concentration, which may vary depending on individual patients.

It should be noted that, although in Figure 15 the total concentration represented by the solid line is shown as gradually declining, it need not be the case according to the instant invention. So long as the solid curve is within the therapeutic effective concentration, slight fluctuations may be tolerable. The concentration towards the end of the regimen is not necessarily lower than that towards the beginning of the regimen.

Also note that the size of the plateau represented by the flat portion of the solid curve need not be limited to 4-12 hours as shown in the illustrative Figure 15.

In an alternative embodiment, the same therapeutic composition as described above may be coated by a layer of delayed-release coating, such that the first IR portion will not start to be released until after a pre-determined period of time, such as the normal 6-10 hours of sleep time. According to this embodiment, the medicine taken by the patient at night, for example, just before sleep, would start to be effective just before the patient wakes up in the morning. This would allow the patient to have an effective therapeutic concentration already in his system when he wakes up in the morning, and immediately participate in his normal daily activities without delay.

Thus the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a sleep-inducing agent; and, (2) a decarboxylase enzyme inhibitor formulated to reach and maintain an optimal plasma concentration at a predetermined time after the administration of the pharmaceutical composition to the patient.

The sleep-inducing agent is advantageous in that it helps to ensure relatively uniform timing between administration and release of the decarboxylase enzyme inhibitor. For example, without the sleep-inducing agent, certain patients may fall sleep quickly after taking the medicine with the decarboxylase enzyme inhibitor, while others may take hours before they finally fall asleep. Assuming the same amount actual sleeping time is needed for both

types of patients (*e.g.*, 7-8 hrs), the level of decarboxylase enzyme inhibitor may reach the designed optimal level only in certain patients just before they wake up. In patients who take longer to fall asleep, the optimal level may have already passed when these patients wake up.

Using a formulation with a sleep-inducing agent, patients will awaken with an effective plasma level of decarboxylase inhibitor and can take a morning dose of levodopa and/or carbidopa (as described above) without having to wait for the decarboxylase enzyme inhibitor to reach an effective level before levodopa starts to take effect.

Alternatively, the pharmaceutical composition with sleeping-inducing agent and decarboxylase enzyme inhibitor may additionally comprise delayed-release IR and delayed CR portions. Specifically: (3) a first delayed immediate-release (DIR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of the predetermined time; and (4) a second delayed controlled release (DCR) portion comprising levodopa and/or its precursor, formulated to release levodopa and/or the precursor at a substantially zero-order release rate over a sustained treatment period after the predetermined time, to maintain the therapeutically effective concentration of levodopa in the patient.

These pharmaceutical compositions, either with or without the levodopa/carbidopa compositions, are suitable for administration to a patient before sleeping. If the sleep-inducing agent and the decarboxylase enzyme inhibitor do not comprise the levodopa / carbidopa composition, the levodopa / carbidopa composition may be separately administered to the patient in the morning upon waking. In this case, the decarboxylase enzyme inhibitor is formulated to reach and maintain an optimal plasma concentration just at or just prior to the wake-up time, *e.g.*, the predetermined time is about the average sleeping time from the administration of the sleep-inducing agent, such as 7 hrs, 8 hrs, 9 hrs, *etc.* In this case, the sleep-inducing agent and the decarboxylase enzyme inhibitor may be a "night pill," while the levodopa / carbidopa extended releasecomposition may be a "morning pill." In PD patients, the sequence of administering the two types of pills (night pill and morning pill) is critical to achieving the optimal therapeutic effect. Both dosage forms may be packaged together, for example, as compliance promoting twin blister packages, making it convenient and clear to the patient about the order and timing of administration of the two types of doses. Optionally, the different dosage forms may be configured differently, *e.g.*, by the appearance of the dosages themselves, such as different colors and/or different shapes, sizes, markings, imprintings, *etc.*, or by labeling used in the packaging.

If the sleep-inducing agent/decarboxylase enzyme inhibitor formulation further comprises the levodopa / carbidopa composition, the levodopa / carbidopa composition is formulated as delayed release formulation, such that levodopa / carbidopa will start to be released just at or just prior to the patient waking up, obviating the need for a separate morning dosage form.

In certain embodiments, the sleep-inducing agent is benzodiazepine (*e.g.*, LIBRIUM®, VALIUM®, HALCION®), Secobarbital (SECONAL®), a prescription sleeping aid medicine (*e.g.*, AMBIEN®, RESTORIL®, DESYREL®, and SONATA®), eszopiclone (*e.g.*, LUNESTA™), or a non-prescription (over-the-counter) sleeping aid medicine (*e.g.*, TYLENOL® PM, EXCEDRIN PM®, UNISOM® / NYTOL® / SLEEPINAL®).

Figure 50 provides an exemplary scheme or drug cycle regarding the release of different components of the subject single dosage formulation. Depending on the specific embodiments involved, not all components are necessarily present. The timings of release are approximate and for illustration purposes only, and may not be to scale. A typical patient for the purpose of this figure follows a routine of waking up around 7 am in the morning and going to sleep around 10-11 pm at night. Specifically, for each portion (*e.g.*, 1st IR, substantial zero-order release, substantial elevating zero-order release, 2nd IR, sleep-inducing agent & decarboxylase inhibitor, *etc.*), the closed circle indicates the approximate start of drug release, and the arrowhead indicates the approximate end or tailing off of the release. For components not starting at about the time of administration, a delayed-release coating may be present to effect the delay. The stool softener, COMT inhibitor, and/or dopamine transport inhibitor, and other auxillary drug components, *etc.*, if present, may be released at any time during the drug cycle, with any effective components (1st IR, substantial zero-order release, 2nd IR, *etc.*), either simultaneously or sequentially (hence the dashed line).

In certain embodiments, a patient can take one AM dose per day, and continue indefinitely if desirable. Alternatively, the patient may take one AM dose when waking up, followed by one PM dose before sleeping, and continue this pattern indefinitely if desirable. The PM dose may contain a sleep-inducing agent & a decarboxylase enzyme inhibitor. In yet another embodiment, the patient may take one PM dose per day, and continue indefinitely if desired. In this embodiment, the PM dose also contains effective components (*e.g.*, carbidopa / levodopa) in delayed-release formulation, such that release profile similar to the left-hand side of Figure 50 (Day 1) is achieved for Day 2.

It should be understood that such release profiles may also be used to divide the

different components into multiple dosage systems (such as a sleep aid, a night-time formulation, and a morning formulation, *etc.*), so long as the overall formulations are designed to release the drugs at or about the times indicated on the scheme.

In certain embodiments, the subject dosage form allows rapid release of drug (*e.g.*, levodopa) in the morning at a rate that results in rapid and reproducible onset of action, reduced frequency of administration, reduced severity of side effects (motor fluctuations). The onset of action may be effected at about 5 minutes, 10 minutes, 15 minutes after the administration, or about 30 minutes, or about 45 minutes, or about 1 hour after the administration of the pharmaceutical composition comprising an immediate-release composition.

In certain embodiments, the ratio of carbidopa (or other equivalent decarboxylase inhibitors) to levodopa is variable, between different individuals / patients, and/or between the different stages of release (*e.g.*, immediate-release vs. substantially zero-order release vs. the optional substantially ascending / rapid rate of release), and/or within each stage of release (*e.g.*, within the zero-order release stage).

Depending on specific situations, the carbidopa : levodopa ratio may be about 1:20, 1:15, 1:10, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, or about 6:1 or more.

The usual daily therapeutic dose of carbidopa is approximately 75 mg per day, but carbidopa apparently fails to elicit adverse effects even at doses of 400 mg per day (Ahlskog, *Hosp. Form.*, **27**: 146, 1992). Thus the total daily dose of carbidopa may be anywhere below about 600 mg, 500 mg, or 400 mg.

For example, to effect a rapid rise of carbidopa concentration in a patient's system, a greater than 1:4 ratio of carbidopa:levodopa may be used (*e.g.*, greater than 1:3, 1:2, 1:1, 2:1, *etc.*). This helps ensure that peripheral decarboxylase activity is substantially inhibited in the treated individual, without regard to any individual differences in peripheral decarboxylase level and/or activity. In contrast, compared to the standard 1:4 ratio, the carbidopa : levodopa ratio may be very low in the second IR portion (*e.g.* less than about 1:10, 1:15, 1:20, *etc.*), or carbidopa may be omitted from this portion altogether, such that a rapid drop in effective levodopa can be effected towards the end of regimen, allowing the treated patient to sleep or rest normally without being substantially affected by the lingering effects of levodopa therapy that can disrupt normal sleep patterns.

In fact, in certain embodiments, the carbidopa : levodopa ratio may vary even within a single release stage. For example, during the substantially zero-order release stage, the ratio

may be closer to 1:4 when entering this stage, and gradually decrease to 1:5, 1:6, 1:8, 1:9, 1:10, *etc.*, such that at the end of this stage, the ratio is substantially smaller than the starting ratio. This effect can be achieved using a number of approaches. For example, carbidopa and levodopa may be mixed together and spun in a container to create a gradient of inhibitor : drug. Alternatively, carbidopa and levodopa may occupy two sides of an imaginal tilted plane dissecting a cylindrical column, such that an increasing or decreasing proportion of the dissolving surface comprises the inhibitor carbidopa. In a related embodiment, the release rate remains constant for the levodopa composition, while the release rate gradually decreases for carbidopa (see **Figure 7**). Yet another alternative is to stack many layers, each with a unique carbidopa:levodopa ratio, *etc.* Obviously, using these methods, the ratio may remain constant for any desired period or periods of time during the stage.

In other embodiments, the invention provides a bioadhesive dosage form that releases the drug at the target absorption site, and is less prone to gastric emptying, thus resulting in a more reproducible and consistent plasma level of levodopa, a drug with a narrow absorption window. In certain embodiments, the bioadhesive layer / patch is used in conjunction with the substantially zero-order release composition.

Another approach to achieving a constant dopamine level in the brain is to work at the level of brain biochemistry. Dopamine in the brain, whether released by a pre-synaptic neuron or supplied by the delivery of levodopa through the brain blood barrier, is removed from the junction by mechanisms of dopamine uptake to stop information transfer. Partial blocking of the dopamine uptake could result in more constant dopamine levels in the brain without the need to modify the levodopa profile in the blood. Methylphenidate, a relatively safe drug used to treat children suffering from Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD), is a dopamine transport inhibitor. Methylphenidate has been used with levodopa in Parkinson's disease patients, resulting, however, in severe dyskinesia and other motor effects of levodopa on the patients, especially when the two drugs are delivered together. Camicioli, *et al.* "Methylphenidate Increases the Motor Effects of L-Dopa in Parkinson's Disease: a Pilot Study," *Clin. Neuropharmacol.* **24(4)**: 208-213, 2001.

However, when dosages are properly calibrated, the detrimental results associated with the co-delivery of levodopa and at least one dopamine transport inhibitor can be avoided and beneficial results achieved. Delivery of dopamine transport inhibitors too early in the levodopa-in-blood release profile enhances the adverse motor effects caused by high levels of dopamine in the brain. However, by properly adjusting the levodopa dose and proper timing

of the dopamine transport inhibitor to block the dopamine transporter, substantially constant levels of dopamine in the brain can be achieved. Preferably, the dopamine transport inhibitor is administered as the dopamine levels start to decrease.

During normal brain function, dopamine is released in the synapse by neuron cells and eliminated by transport proteins. Co-treatment with a drug that inhibits the transport protein allows the dopamine to reside longer in the brain, thereby making the effective drug troughs shallow. Additionally, the efficient use of the method lowers concentration peaks by lowering levodopa dosing levels. Proper timing of the co-treatment with the two drugs is essential. Administering the dopamine transport inhibitor too early may result in peaks of brain dopamine and problems of dyskinesia. Administering the dopamine transport inhibitor too late may result in too little advantage, because the dopamine levels in the brain will have already been depleted by the normal elimination processes. Proper timing of the transport inhibitor delivery to slightly after the predicted peak in brain dopamine concentration and keeping the inhibitor in place for some time extends the time that effective concentrations of the dopamine are present in the brain. However, extending the time of the transport inhibition too long can have deleterious effects, since it may lead to too high a dopamine concentration as additional levodopa is administered.

Thus, in certain embodiments, the invention provides dosage forms comprising levodopa and at least one dopamine transport inhibitor. The administration of the dopamine transport inhibitor may be delayed such that release coincides with the time the dopamine concentration level starts to decrease. The dopamine transport inhibitor is a compound capable of delaying the dopamine transporter from removing dopamine from the brain. In other words, the dopamine transport inhibitor precludes or diminishes the removal rate of dopamine by the dopamine transporter, thereby prolonging a concentration of dopamine in the brain. Dopamine transporter inhibitors include, but are not limited to, methylphenidate. In the formulation of the invention, methylphenidate may be present in an amount about 1 mg to about 60 mg, preferably from 1 mg to about 15 mg, more preferably, from about 5 mg to about 10 mg, and most preferably methylphenidate may be present in an amount of about 10 mg per dose.

In certain embodiments, a levodopa metabolic precursor like the levodopa ethyl ester of U.S. Pat. No. 5,840,756 (incorporated herein by reference) may be substituted for some or all of the levodopa in the various embodiments of the invention. Typically, levodopa is present in an amount from about 50 mg to about 300 mg, preferably from about 100 mg to

about 200 mg and, more preferably, levodopa is present in an amount of about 100 mg to about 150 mg per dose. The amount of levodopa may also be adjusted accordingly if any of the other formulations described below are adapted for use in the instant invention.

As discussed above, the timing of the administration of the individual ingredients of the composition of the invention is important to achieve the desired leveling of peaks and troughs of dopamine concentrations when treating Parkinson's disease. Generally, it is desirable to administer levodopa and, optionally, a decarboxylase enzyme inhibitor, prior to the administration of at least one dopamine transporter inhibitor. Alternatively, the levodopa, decarboxylase enzyme inhibitor, and dopamine transporter inhibitor of the composition may be administered concurrently as a unit dose or co-administered as several doses. Each ingredient, however, may be formulated either as an immediate release formulation or sustained release formulation with or without a time delay. The ratio of each ingredient may also vary between the first (and second, if present) immediate-release and the substantially zero-order release dose.

In certain embodiments, levodopa may be administered as an immediate-release formulation or a sustained-release delivery formulation wherein the levodopa is released over about 1 to about 4 hours. The decarboxylase enzyme inhibitor may be dosed as an immediate-release drug delivery formulation or a sustained-release delivery formulation (with levodopa or independently) wherein the decarboxylase enzyme inhibitor is released over about 1 to about 4 hours. Typically, the dopamine transporter inhibitor is formulated as an immediate-release formulation which releases after about a 2-hour to about 7-hour delay, and preferably after about a 3- to about 5-hour delay. Alternatively, the dopamine transporter inhibitor may be formulated as a sustained-release delivery formulation which releases over one to six hours after about a 1- to about 7-hour delay.

In certain embodiments, the subject pharmaceutical composition is formulated for variable dosing, such as customized dosing for individual patients.

Another aspect of the invention relates to a decayboxylase enzyme inhibitor (*e.g.*, carbidopa or its pro-drug) formulation for extended release of the inhibitor over a prolonged period, optionally at a selected target site, such as a site proximal to the small intestine, *e.g.*, proximal small intestine.

Currently available levodopa/carbidopa formulations contain fixed levels of both compounds (*e.g.*, levodopa:carbidopa ratio of 10:1 and 4:1, *etc.*). A higher frequency of side effects (especially nausea and vomiting) may arise when the levodopa:carbidopa ratio is

higher. Studies have also shown that about 75 to 150 mg of carbidopa seems to be needed daily to inhibit the peripheral dopa decarboxylase fully (Jaffe, *Adv. Neurol.* **2**: 161-172, 1973). However, repeated administration of carbidopa was needed to completely inhibit the decarboxylase activity. Furthermore, carbidopa has a narrow absorption window and is absorbed mainly in the proximal small intestine. About 70% of an administered dose of carbidopa is absorbed, and gastric emptying of the drug plays an important role in its absorption.

The instant invention provides an extended release decarboxylase enzyme inhibitor (*e.g.*, carbidopa) formulation that releases the inhibitor at the target absorption site and at a substantially constant rate, thereby significantly inhibiting decarboxylation of levodopa in extracerebral tissues, resulting in increased transport of levodopa to the brain.

Thus, In certain embodiments, the invention provides a bioadhesive oral dosage form that releases a continuous supply of inhibitor (*e.g.*, carbidopa) to a desired absorption site (*e.g.*, the proximal small intestine), *e.g.*, yielding a consistent carbidopa release to the systemic blood circulation for a prolonged period (*e.g.*, 10-12 hours). Because decarboxylase enzyme levels are unevenly distributed along the intestinal tract, a continuous supply of carbidopa overnight more effectively inhibits the peripheral dopa decarboxylase. Such a strategy can be used in combination with administration of levodopa dosage forms. For example, a strategy of pre-dosing with a carbidopa extended-release formulation prior to administration of a levodopa formulation, *e.g.*, levodopa-carbidopa extended release tablet, further improves the performance of the levodopa formulation by facilitating the maintenance of stable levodopa plasma levels, leading to more constant dopaminergic stimulation. In addition, pre-dosing with the subject carbidopa extended-release formulation prior to medication with levodopa formulation such as levodopa-carbidopa product may also help prevent early morning "off medication" dyskinesias and dystonia.

In certain embodiments, the subject pharmaceutical composition increases the bioavailability of the subsequently administered levodopa compositions, by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 100% or more. Bioavailability may be measured by AUC_{0-24} using any art-recognized methods, such as according to the examples described herein.

The carbidopa dosage form may be designed to be administered in the evening time following a meal to take advantage of reduced gastric emptying and motility associated with the fed state and sleeping. The efficacy of subsequent morning dosing with a levodopa

formulation, *e.g.*, a (multilayer) extended release (tablet) formulation, such as the subject Levodopa/Carbidopa Multilayer Extended Release Tablet 200mg/50mg formulation "D," may be improved by pre-dosing with the subject carbidopa trilayer extended release tablet (*e.g.*, the 100 mg) formulation.

Thus this aspect of the invention provides a pharmaceutical composition comprising: a decarboxylase enzyme inhibitor formulated to provide an effective plasma concentration of the decarboxylase enzyme inhibitor over a predetermined extended period of time after the administration of the pharmaceutical composition to the patient. Optionally, the pharmaceutical composition further comprises: (1) one or more bioadhesive layers, (2) one or more bioadhesive compositions incorporated in the pharmaceutical composition, or (3) one or more bioadhesive compositions incorporated as layers in the pharmaceutical composition, for example, as a multilayer tablet. These subject pharmaceutical compositions may be useful for preferentially targeting the release of the decarboxylase enzyme inhibitor at a target absorption site.

In certain embodiments, the pharmaceutical composition is substantially free of levodopa or its metabolic precursor thereof.

In certain embodiments, the pharmaceutical composition is substantially free of decarboxylase enzyme inhibitors formulated for immediate release, *e.g.*, to release an effective amount of decarboxylase inhibitor within about 1-2 hours of administration, or even within 30 minutes of administration. Thus, in certain embodiments, less than 50%, less than 25%, less than 15% or even less than 10% of the decarboxylase inhibitor in the formulation is released within the first hour, or even the first two hours, after administration of the formulation. Similarly, in certain embodiments, less than 50%, less than 25%, less than 15% or even less than 10% of the decarboxylase inhibitor in the formulation is released within the first hour, or even the first two hours, after release of the decarboxylase inhibitor commences. For example, the pharmaceutical composition may release the effective components (*e.g.*, decarboxylase inhibitor, such as carbidopa) at a substantially linear / constant rate over the entire predetermined extended period of time after the administration of the pharmaceutical composition to the patient. Alternatively, although the release rate is not constant or linear over the entire period of time, it is at least linear / constant over one or more portions of the entire period, with rates being the same or different between different portions.

Indeed, in certain embodiments, the release profile of the decarboxylase enzyme inhibitor during the entire predetermined extended period of time may take numerous forms,

so long as the decarboxylase enzyme inhibitor is formulated to provide a substantially constant effective plasma concentration (*e.g.*, the highest serum concentration is no more than 50% or 100% greater than the lowest serum concentration) during a period starting at least about 4 hours after administration to the patient, at least about 5 hours after administration to the patient, at least about 6 hours after administration to the patient, at least about 7 hours after administration to the patient, or at least about 8 hours after administration to the patient.

Alternatively, the decarboxylase enzyme inhibitor is formulated to provide a substantially constant effective plasma concentration, no later than about 4 hours before the patient's waking, no later than about 5 hours before the patient's waking, no later than about 6 hours before the patient's waking, no later than about 7 hours before the patient's waking, no later than about 8 hours before the patient's waking, *etc.*

These embodiments may be achieved by using one or more delayed release and/or extended release formulations of the decarboxylase enzyme inhibitors described herein. For example, using a controlled-release polymer coating, the release rate of the decarboxylase enzyme inhibitor may be controlled to last a desired period of time (*e.g.*, 6 hours, 8 hours, 10 hours, 12 hours, *etc.*) at a substantially constant rate. Using a delayed-release and/or enteric coating, the release of the decarboxylase enzyme inhibitor may be delayed until several hours (*e.g.,* 1 hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 7 hrs, *etc.*) after the patient goes to sleep, and/or becomes substantially constant at least several hours (*e.g.*, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 7 hrs, *etc.*) before the patient wakes up.

In certain embodiments, the predetermined extended period of time (*e.g.*, between the administration of the composition before the patient goes to sleep, and when (or shortly after) the patient wakes up) is about 7-14 hours, 8-14 hours, or about 9-13 hours, or about 10-12 hours, or about 11 hours. The administration time need not be just before sleeping. For example, it can be shortly before, with, or right after the last meal of the day, or some other convenient time. A preferred administration time is shortly before, with, or right after the last meal of the day, in order to take advantage of reduced gastric emptying and motility associated with the fed state and sleeping. Thus, generally, the formulation is designed to be administered at a time such that, whether release of the decarboxylase inhibitor begins immediately or is delayed for a period of time, the decarboxylase inhibitor is released while the patient sleeps (*e.g.*, commencing at least 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 7 hrs, *etc.* before the patient wakes) continuing up to about a time where the patient wakes, or even for a period of time thereafter, such that there is an effective plasma level of the decarboxylase inhibitor in

the patient when the patient awakens. Thus, the period of release of the decarboxylase inhibitor is extended or delayed for a formulation designed to be taken substantially in advance of the onset of sleep (*e.g.*, at dinner) as compared to a formulation designed to be taken just before onset of sleep.

In certain embodiments, the decarboxylase enzyme inhibitor is released at a substantially constant rate over the predetermined extended period of time. "Substantially constant rate" refers to a release rate that does not substantially vary, *e.g.*, with no more than about 50% or 100% variations between the highest and lowest rates.

In certain embodiments, the subject decarboxylase enzyme inhibitor is formulated in a partially exposed core between two bioadhesive layers. For example, in a trilayer tablet design that resembles a sandwich, the first and third layer may be bioadhesive layers, each covering at least a portion of the second layer – the decarboxylase enzyme inhibitor core. The inhibitor may be released through the partial surface not covered by the bioadhesive layers.

However, the composition need not be formulated as a tablet. There could be many other designs where two bioadhesive layers partially cover the inhibitor core. For example, a cylinder-shaped or bead-shaped core may be covered by 2 patches / layers of bioadhesive layers, which bioadhesive layers can, but need not, be of the same size or symmetrically positioned with respect to the core. The exposed surface of the core (and thus the inhibitor release rate) may be substantially constant or may change over time (*e.g.*, increase or descrease, in a linear or non-linear fashion, *etc.*), as the core erodes.

In certain embodiments, the subject pharmaceutical composition is selectively released at a target absorption site, such as the proximal small intestine, through the use of appropriate bioadhesive layers.

In certain embodiments, the subject pharmaceutical composition further comprises a sleep-inducing agent. This is useful if the subject composition is to be administered to the patient before sleeping. Any sleep-inducing agent(s) described herein may be used for this purpose.

In certain embodiments, the subject pharmaceutical composition further comprises one or more of: a dopaminergic and anti-cholinergic agent, such as amantadine; an anti-cholinergic agent, such as trihexyphenidyl, benztropine, ethoproprazine, or procyclidine; a dopamine agonist, such as: apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, or ropinirole; a MAO-B (monoamine oxidase B) inhibitor, such as: selegiline or deprenyl; a COMT inhibitor, such as: CGP-28014, entacapone, or tolcapone; a muscle

relaxant, such as baclofen; a sedative, such as Clonazepam; an anticonvulsant agent, such as carbamazepine; a dopamine reuptake inhibitor, such as tetrabenazine; a dopamine blocker, such as haloperidol; a β-blocker, such as: propranolol; a carbonic anhydrase inhibitor, such as: acetalzolamide or methazolamide; a narcotic agent, such as codeine; a GABAergic agent, such as gabapentin; an alpha antagonist, such as clonidine; a stool softener, such as: bran or psyllium, methylcellulose, polycarbophil, docusate, docusate sodium and casanthranol combination, magnesium hydroxide, magnesium citrate, sorbitol, polyethylene glycol solution, lactulose, lubiprostone or other osmotic or stimulant laxatives, and a natural stool softener; or a dopamine transport inhibitor, such as those described herein.

In certain embodiments, the decarboxylase enzyme inhibitor is carbidopa, a carbidopa prodrug, benserazide, methylphenidate, or a combination thereof.

In certain embodiments, the total dose of the decarboxylase enzyme inhibitor is about 25 – 300 mg, or about 75 – 200 mg, or about 100 mg.

In certain embodiments, the one or more (bioadhesive) layers may include any of the bioadhesive materials described herein, preferably those that selectively target the lining of small intestine, such as proximal small intestine. Exemplary bioadhesive materials may be selected from chitosan, hyaluronic acid, hyaluran, thiomers, poly(methylvinylether-co-malic anhydride), polyamides, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, carbopols, carbomers, polyvinylpyrrolidone, polyglycolides, polyurethanes, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends and copolymers thereof. In a preferred embodiment, the pharmaceutical composition comprising one or more bioadhesive layers including poly(fumaric-co-sebacic) anhydride.

In certain embodiments, the one or more bioadhesive layers comprise bioadhesive materials having a catechol moiety.

In certain embodiments, the bioadhesive materials comprise a mixture of a material and a compound comprising a catechol moiety selected from L-Dopa, D-dopa, dopamine, or carbidopa.

In certain embodiments, the bioadhesive materials are selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid),

poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends, and/or copolymers thereof.

In certain embodiments, the one or more bioadhesive layers comprise bioadhesive material covalently functionalized with a catechol moiety.

In certain embodiments, the catechol moiety is derived from L-dopa, D-dopa, dopamine, or carbidopa.

In certain embodiments, the biolayers comprise SPHEROMER™ I, SPHEROMER™ II, SPHEROMER™ III, and/or SPHEROMER™ IV.

In certain embodiments, the one or more bioadhesive layers comprises an additive that stabilizes the bioadhesive layers from erosion, dissolution or both, wherein at least 50% by weight of a 1 mm thick film of the bioadhesive layers remain after 12 hours in a buffered pH 4.5 dissolution bath.

In certain embodiments, the bioadhesive layers comprise an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

In certain embodiments, the subject pharmaceutical composition is suitable for human treatment, or for veterinary treatment of a non-human animal. Such non-human animal include both domestic animals and livestock, raised either as laboratory animals, pets or zoo animals, or for commercial purposes. Examples are rodents such as mice, rats, hamsters, or rabbits; dogs; cats; cattle; horses; sheep; hogs; and goats.

Another aspect of the invention provides a method for making the pharmaceutical compositions with one or more features as described above.

For example, one aspect of the invention provides a method of making a pharmaceutical composition, which may be useful for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising combining the decarboxylase enzyme inhibitor with one or more bioadhesive layers into a single dosage form.

In certain embodiments, the pharmaceutical composition is substantially free of levodopa.

In certain embodiments, the pharmaceutical composition is substantially free of immediate release formulation of decarboxylase enzyme inhibitors.

In certain embodiments, the decarboxylase enzyme inhibitor is formulated to provide a constant effective plasma concentration starting at least about 4 hours after administration to

the patient.

Another aspect of the invention provides a method for using the pharmaceutical compositions with one or more features as described above, in treating a movement disorder, such as Parkinson's disease.

For example, one aspect of the invention provides a method of treating a patient, such as one suffering from Parkinson's disease and/or another movement disorder, comprising administering to the patient any of the subject pharmaceutical compositions described herein that comprises (1) a decarboxylase enzyme inhibitor formulated to provide an effective plasma concentration of the decarboxylase enzyme inhibitor over a predetermined extended period of time after the administration of the pharmaceutical composition to the patient, and (2) one or more bioadhesive layers for preferentially targeting the release of the decarboxylase enzyme inhibitor at a target absorption site.

In certain embodiments, the pharmaceutical composition is administered before the patient goes to sleep.

In certain embodiments, the pharmaceutical composition is administered shortly before, with, or after the patient's last meal before going to sleep.

In certain embodiments, the method further comprises administering a second pharmaceutical composition comprising levodopa or a metabolic precursor thereof about 6-12 hours after, about 7-11 hrs after, about 8-10 hrs after, about 9 hrs after administration of the extended release decarboxylase inhibitor formulation, *etc.*

Another aspect of the invention provides a packaged pharmaceutical composition, which may be useful for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first pharmaceutical composition comprising a decarboxylase enzyme inhibitor formulated to provide an effective plasma concentration of the decarboxylase enzyme inhibitor over a predetermined extended period of time after the administration of the pharmaceutical composition to the patient, and one or more bioadhesive layers for preferentially targeting the release of the decarboxylase enzyme inhibitor at a target absorption site; and (2) a second pharmaceutical composition comprising levodopa or a metabolic precursor thereof.

According to this aspect of the invention, the first pharmaceutical composition acts as a pre-dose, which preferably is substantially free of levodopa, and/or substantially free of immediate release formulation of decarboxylase enzyme inhibitors. Optionally, the decarboxylase enzyme inhibitor is formulated to provide a constant effective plasma

concentration starting at least about 4 hours after administration to the patient.

In certain embodiments, the first and/or the second pharmaceutical compositions are packaged separately as individual doses. For example, the package may comprise at least one dose each of the first and the second pharmaceutical compositions. Alternatively, there may be multiple doses of first and second pharmaceutical compositions in the same package, sufficient for treating a patient for a desired treatment period, such as a week, a month, 2 months, 3 months, 6 months, 1 year, *etc.*

In certain embodiments, the first and the second pharmaceutical compositions are differentiated by color, shape, marking, imprinting, and/or size, *etc.*

In certain embodiments, the subject packaged pharmaceutical composition may further comprise an instruction that instructs a patient to take the first pharmaceutical composition before sleep, and to take the second pharmaceutical composition after waking.

All the subject preparations and methods can be used as part of the treatments for human and/or other animal subjects. In addition to humans, other animal subjects to which the invention is applicable extend to both domestic animals and livestock, raised either as laboratory animals, pets or zoo animals, or for commercial purposes. Examples are rodents such as mice, rats, hamsters, or rabbits; dogs; cats; cattle; horses; sheep; hogs; and goats.

In certain embodiments, the method includes administering, conjointly with the subject pharmaceutical composition, one or more of other therapeutic compositions useful for the treat-ment of diseases, for which levodopa/carbidopa or pramipexole is indicated for. For example, in the case of treating Parkinson's Disease and certain movement disorders, levodopa/carbidopa or pramipexole may be co-administered with a dopamine precursor, a dopaminergic agent, a dopaminergic and anti-cholinergic agent, an anti-cholinergic agent, a dopamine agonist, a MAO-B (monoamine oxidase B) inhibitor, a COMT (catechol O-methyltransferase) inhibitor, a muscle relaxant, a sedative, an anticonvulsant agent, a dopamine reuptake inhibitor, a dopamine blocker, a β-blocker, a carbonic anhydrase inhibitor, a narcotic agent, a GABAergic agent, or an α antagonist.

In certain embodiments, the method includes administering, conjointly with the pharmaceutical composition, one or more of physical therapy, occupational therapy, or speech / language therapy.

An agent to be administered conjointly with a subject compound may be formulated together with a subject compound as a single pharmaceutical preparation, *e.g.*, as a pill or other medicament including both agents, or may be administered as a separate pharmaceutical

preparation.

Another aspect of the invention provides a packaged pharmaceutical composition, comprising the subject pharmaceutical composition in an amount sufficient to treat or prevent a movement disorder in a patient, which may additionally include a pharmaceutically acceptable carrier, and instructions (written and/or pictorial) describing the use of the formulation for treating the patient, wherein the patient suffers from ataxia, corticobasal ganglionic degeneration (CBGD), dyskinesia, dystonia, tremors, hereditary spastic paraplegia, Huntington's disease, multiple system atrophy, myoclonus, Parkinson's disease, progressive supranuclear palsy, restless legs syndrome, Rett syndrome, spasticity, Sydenham's chorea, other choreas, athetosis, ballism, stereotypy, tardive dyskinesia/dystonia, tics, Tourette's syndrome, olivopontocerebellar atrophy (OPCA), diffuse Lewy body disease, hemibalismus, hemi-facial spasm, restless leg syndrome, Wilson's disease, stiff man syndrome, akinetic mutism, psychomotor retardation, painful legs moving toes syndrome, a gait disorder, a drug-induced movement disorder, or other movement disorder.

In certain preferred embodiments, the movement disorder is Parkinson's disease.

Certain general features of the invention are further elaborated in the sections below.

II. *Definitions*

For convenience, certain terms employed in the specification, examples, and appended claims are collected here. All other terms have their ordinary meanings as understood by a skilled artisan.

As used herein, "about" means within the pharmaceutically acceptable limits found in the United States Pharmacopia (USP-NF 21), 2003 Annual Edition, or available at the USP website, for amount of active pharmaceutical ingredients. With respect to blood levels, "about" means within FDA acceptable guidelines.

The term "adrenergic" refers to neurotransmitters or neuromodulators chemically related to adrenaline (epinephrine) or to neurons which release such adrenergic mediators. Examples are dopamine, norepinephrine, and epinephrine. Such agents are also referred to as catecholamines, which are derived from the amino acid tyrosine.

As generally used herein, "modified" refers to monomers or polymers which have undergone a chemical reaction.

As generally used herein "bioadhesives" or "bioadhesive materials" refer to the bioadhesive polymers and bioadhesive compositions disclosed herein, including materials

that contain one or more additional components in addition to the bioadhesive polymers and bioadhesive compositions of the invention. Bioadhesives also include blends of one or more bioadhesive polymers or blends disclosed herein with one or more other (bioadhesive or non-bioadhesive) polymers or blends. In certain instances, the term "bioadhesive polymers" is used to refer to both compositions where the polymer itself is bioadhesive, as well as compositions where a non- or poorly bioadhesive polymer is combined with a compound that imparts bioadhesive properties to the composition as a whole, as described in detail herein.

"Bioadhesive polymers" is also used to refer to specific polymer compositions including polyanhydride copolymers of fumaric anhydride and sebacic anhydride reacted through polycondensation (as described in U.S. Patent No. 5,955,096 to Mathiowitz *et al.* and for an example SPHEROMER™ I[p(FASA) (1:4)]), anhydride oligomers, such as fumaric anhydride oligomer, and metal oxides, such as CaO, ferric oxide, magnesium oxide, titanium dioxide (as described in U.S. Patent No. 5,985,312 to Jacob *et al.*, and for an example SPHEROMER™ II), L-DOPA grafted onto butadiene maleic anhydride at 95% substitution efficiency (L-DOPA-BMA) (as described in WO 2005/056708 to Spherics, Inc. and for an example SPHEROMER™ III), and carbidopa grafted onto butadiene maleic anhydride (as described in PCT/US06/24352, Spherics, Inc., and, for an example, SPHEROMER™ IV).

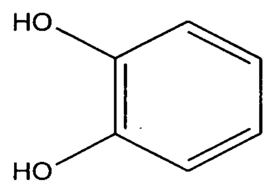
As used herein "bioadhesion" generally refers to the ability of a material to adhere to a biological surface for an extended period of time. Bioadhesion requires a contact between the bioadhesive material and a surface, for example, where the bioadhesive material penetrates into the crevice of the surface (*e.g.* tissue and/or mucus) and chemical bonds form. The amount of bioadhesive force is affected by both the nature of the bioadhesive material, such as a polymer, and the nature of the surrounding medium. Adhesion of materials to tissues may be achieved by (i) physical or mechanical bonds and/or (ii) secondary chemical bonds (*e.g.*, ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bioadhesive properties, consist of dispersive interactions (*e.g.*, Van der Waals interactions) and stronger specific interactions, which include hydrogen bonds and ionic bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are hydroxyl (-OH) and carboxylic acid groups (-COOH). Bioadhesive forces are measured in units of N/m^2. These forces are preferably determined by methods defined in U.S. Patent No. 6,197,346 to Mathiowitz *et al.* Bioadhesive forces, especially those exhibited by tablets, can also be measured using a Texture Analyser, such as the TA-TX2 Texture Analyser (Stable

Micro Systems, Haslemer, Surrey, UK). As described by Michael J. Tobyn *et al* in *Eur. J. Pharm. Biopharm.*, 41(4):235-241 (1995), a mucoadhesive tablet is attached to a probe on the texture analyzer and lowered until it contacts pig gastric tissue, which is attached to a tissue holder and exposed to liquid at 37 °C to simulate gastric medium. A force is applied for a set period of time and then the probe is lifted at a set rate. Area under the force/distance curve calculations are used to determine the work of adhesion. (See also Michael J. Tobyn *et al.*, *Eur. J. Pharm. Biopharm.*, 42(1):56-61 (1996) and David S. Jones, *et al.*, *International J. Pharmaceutics*, 151: 223-233 (1997)).

The term "biogenic amines" refers to a class of neurotransmitters which includes catecholamines (*e.g.*, dopamine, norepinephrine, and epinephrine) and serotonin.

As generally used herein "blend" refers to a mixture of two or more polymers or a mixture of one or more polymers with one or more low molecular weight additives containing a catechol functionality. The mixture can be homogeneous or heterogeneous.

As used herein "catechol" refers to a compound with a molecular formula of $C_6H_6O_2$ and the following structure:



Catechol

Bioadhesive materials contain a polymer with a catechol functionality or a polymer blended with catechol or a catechol derivative. For materials that contain polymers that have been modified with a catechol functionality, the molecular weight of the bioadhesive materials and percent substitution of the polymer with the aromatic compound may vary greatly. The degree of substitution varies based on the desired adhesive strength, it may be as low as 10%, 20%, 25%, 50%, or up to 100% substitution. On average at least 50% of the monomers in the polymeric backbone are substituted with at least one aromatic group. Preferably, 75-95% of the monomers in the backbone are substituted with at least one aromatic group or a side chain containing an aromatic group. In the preferred embodiment, on average 100% of the monomers in the polymeric backbone are substituted with at least one aromatic group or a side chain containing an aromatic group. The resulting bioadhesive material is a polymer with a molecular weight ranging from about 1 to 2,000 kDa, preferably 1 to 1,000 kDa, more preferably 10 to 1,000 kDa, most preferably 100 to 1,000 kDa. For

materials in which a polymer has been blended with catechol or a catechol derivative, the ratio of polymer to catechol can be varied in order to vary the bioadhesive properties of the material. The catechol or catechol derivative can be present in an amount from about 0.5% to about 95% by weight of the polymer, typically about 10% to about 75%, preferably about 10% to about 50% and more preferably about 10% to about 30%.

In certain embodiments of the invention, a polymer may be functionalized by covalently attaching catechol moieties or compounds comprising catechol moieties. Alternatively, a compound comprising a catechol moiety may be blended with a polymer to form a simple mixture with no covalent association between the catechol moieties and the polymer.

The term "catecholamines" refers to neurotransmitters that have a catechol ring (*e.g.*, a 3,4-dihydroxylated benzene ring). Examples are dopamine, norepinephrine, and epinephrine.

The term "cholinergic" refers to neurotransmitters or neuromodulators chemically related to choline or to neurons which release such cholinergic mediators.

The term "Degree of Fluctuation (DFL)" as used herein is expressed as :

$$DFL = (C_{max} - C_{min})/C_{avg}$$

produced by ingestion of the the composition of the invention or the t.i.d comparator.

The term "C_{max}" as used herein means maximum plasma concentration of pramipexole achieved by the ingestion of the composition of the invention or the t.i.d comparator. The term "C_{min}" as used herein means minimum plasma concentration of pramipexole achieved by the ingestion of the composition of the invention or the t.i.d comparator. The term "C_{avg}" as used herein means average plasma concentration of pramipexole achieved by the ingestion of the composition of the invention or the t.i.d comparator. C_{avg} is calculated by AUC_{0-24} over a 24 hours intervals divided by 24.

The term "T_{max}" as used herein means the time to achieve maximum plasma concentrations produced by ingestion of of the composition of the invention or the t.i.d comparator. The term "AUC_{0-24}" as used herein means the area under the plasma concentration-time curve, as calculated by the trapezoidal rule over the 24 hour interval for all the formulations.

As used in this application, the term "C_{min}" and "trough levels" should be considered synonyms. Likewise, "C_{max}" and "peak levels" should be considered synonyms.

The term "dopaminergic" refers to neurotransmitters or neuromodulators chemically

related to dopamine or to neurons which release such dopaminergic mediators.

The term “dopamine” refers to an adrenergic neurotransmitter, as is known in the art.

The term “ED_{50}” means the dose of a drug which produces 50% of its maximum response or effect.

An "effective amount" of, *e.g.*, a movement disorder pharmaceutical composition, with respect to the subject method of treatment, refers to an amount of the pharmaceutical composition in a preparation which, when applied as part of the subject dosage regimen brings about the desired correction / suppression of the movement disorder (*e.g.*, dyskinesis and/or bradykinesis) according to clinically acceptable standards.

The term “LD_{50}” means the dose of a drug which is lethal in 50% of test subjects.

The term "lethal therapeutic index" refers to the therapeutic index of a drug defined as LD_{50}/ED_{50}.

The term “metabolites” refers to active derivatives produced upon introduction of a compound into a biological milieu, such as a patient.

The term “orally deliverable” herein means suitable for oral, including peroral and intra-oral (*e.g.*, sublingual or buccal) administration, but tablets of the present invention are adapted primarily for peroral administration, *i.e.*, for swallowing, typically whole or broken, with the aid of water or other drinkable fluid.

A "patient," “individual,” or "subject" to be treated by the subject method can mean either a human or non-human animal.

The term “prevent,” “preventing,” or “prevention” as used herein means reducing the probability / risk of developing a condition in a subject (*e.g.*, a human), or delaying the onset of a condition in the subject, or lessening the severity of one or more symptoms of a condition (*e.g.*, a movement disorder) that may develop in the subject, or any combination thereof.

The term “prodrug” is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present invention. A common method for making a prodrug is to include selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of

protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. Protective Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991).

The term "SeD_{50}" means the dose of a drug which is produces a particular side-effect in 50% of test subjects.

The term "side-effect therapeutic index" refers to the therapeutic index of a drug defined as SeD_{50}/ED_{50}.

A "subject" herein is an animal of any species, preferably mammalian, most preferably human. Conditions and disorders in a subject for which a particular agent is said herein to be "indicated" are not restricted to conditions and disorders for which the agent has been expressly approved by a regulatory authority, but also include other conditions and disorders known or believed by a physician to be amenable to treatment with the agent.

"Solid fraction" is the ratio of absolute to apparent density of a compact of the starch. A "compact" herein is a compressed tablet, prepared for example on a tablet press, consisting only of a sample of starch for which it is desired to measure tensile strength. A "solid fraction representative of the tablet" is a solid fraction selected to be similar to the solid fraction of tablets prepared according to the invention. Typically a solid fraction of about 0.75 to about 0.85, illustratively 0.8, will be selected.

The term "statistically significant" as used herein means that the obtained results are not likely to be due to chance fluctuations at the specified level of probability. The two most commonly specified levels of significance are 0.05 (p=0.05) and 0.01 (p=0.01). The level of significance equal to 0.05 and 0.01 means that the probability of error is 5 out of 100 and 1 out of 100, respectively.

By "transdermal patch" is meant a system capable of delivery of a drug to a patient via the skin, or any suitable external surface, including mucosal membranes, such as those found inside the mouth. Such delivery systems generally comprise a flexible backing, an adhesive and a drug retaining matrix, the backing protecting the adhesive and matrix and the adhesive holding the whole on the skin of the patient. On contact with the skin, the drug-retaining matrix delivers drug to the skin, the drug then passing through the skin into the patient's system.

The term "treat," "treating," or "treatment" as used herein means to counteract a medical condition (*e.g.*, a movement disorder) to the extent that the medical condition is improved according to clinically acceptable standard(s). For example, "to treat a movement disorder" means to improve the movement disorder or relieve symptoms of the particular

movement disorder in a patient, wherein the improvement and relief are evaluated with a clinically acceptable standardized test (*e.g.*, a patient self-assessment scale) and/or an empirical test (*e.g.*, PET scan). "Treatment" herein embraces prophylactic treatment unless the context requires otherwise.

The term "water-soluble" herein means having solubility of at least about 10 mg/ml. Unless otherwise specified, "solubility" herein means solubility in water at 20-25°C at any physiologically acceptable pH, for example at any pH in the range of about 4 to about 8. In the case of a salt, reference herein to solubility in water pertains to the salt, not to the free base form of pramipexole.

III. *Exemplary Uses of the Dosage Forms*

In various embodiments, the present invention contemplates modes of treatment and/or prophylaxis (*e.g.*, treating or preventing the development of symptoms in high-risk populations), which utilize one or more of the subject dosage forms for decreasing or overcoming the defects in a movement disorder patient. The improvement and/or restoration of mental or physical state in an organism has positive behavioral, social, and psychological consequences.

For example, Parkinson's disease is the second most common neurodegenerative disorder, affecting nearly 1 million people in North America. The disease is characterized by symptoms such as muscle rigidity, tremor and bradykinesia. Early studies of Parkinson's disease showed unusual inclusions in the cytoplasm of neurons (*i.e.*, Lewy bodies), occurring predominantly in the substantia nigra, which innervate the striatal region of the forebrain. Although Lewy bodies were also found in other neurodegenerative conditions, the presence of Lewy bodies in Parkinson's disease is accompanied by cell loss in the substantia nigra. This cell loss is considered to be the defining pathological feature of Parkinson's disease.

Epidemiological studies have reported geographic variation in Parkinson's disease incidence, leading to the search for environmental factors (Olanow and Tatton, *Ann. Rev. Neurosci.* **22**: 123-144, 1998). The recent discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxin causes a Parkinson's-like syndrome indistinguishable from the idiopathic disease suggests that Parkinson's disease may be caused by environmental factors (*e.g.*, toxins and causative agents). (See *e.g.*, Langston, *Ann. Neurol.* **44**: S45-S52, 1998).

Recent research has also identified genes associated with Parkinson's disease (Mizuno

et al., *Biomed. Pharmacother.* **53(3)**: 109-116, 1999; Dunnett and Bjorklund, *Nature* **399 (6738 Suppl)**: A32-A39, 1999); namely, the α-synuclein gene (Polymeropouos *et al.*, *Science* **276**: 2045-2047, 1997), the parkin gene (Kitada *et al.*, *Nature* **392**: 605-608, 1998), and the UCH-L1 thiol protease gene (Leroy *et al.*, *Nature* **395**: 451-452, 1998). Although additional chromosomal loci associated with the disease state have been identified, these chromosomal loci have not been analyzed at the molecular level. At present, the biochemical roles played by these gene products in both normal cells and in diseased neurons remain ambiguous, and no gene therapy protocols involving their use have been developed.

Furthermore, Parkinson's disease is associated with the progressive loss of dopamine neurons in the ventral mesencephalon of the substantia nigra (Shoulson, *Science* **282**: 1072-1074, 1998), which innervates the major motor-control center of the forebrain, the striatum. Although a gradual decline in the number of neurons and dopamine content of the basal ganglia is normally associated with increasing age, progressive dopamine loss is pronounced in people suffering from Parkinson's disease, resulting in the appearance of symptoms when about 70-80% of striatal dopamine and 50% of nigral dopamine neurons are lost (Dunnett and Bjorklund, *supra*). This loss of dopamine-producing neurons resulting in a dopamine deficiency is believed to be responsible for the motor symptoms of Parkinson's disease.

Although the cause of dopaminergic cell death remains unknown, it is believed that dopaminergic cell death is affected by a combination of necrotic and apoptotic cell death. Mechanisms and signals responsible for the progressive degeneration of nigral dopamine neurons in Parkinson's disease have been proposed (Olanow *et al.*, *Ann. Neurol.* **44**: S1-S196, 1998), and include oxidative stress (from the generation of reactive oxygen species), mitochondrial dysfunction, excitotoxicity, calcium imbalance, inflammatory changes and apoptosis as contributory and interdependent factors in Parkinson's disease neuronal cell death.

Apoptosis (*i.e.*, programmed cell death) plays a fundamental role in the development of the nervous system (Oppenheim, *Ann. Rev. Neurosci.* **14**: 453-501, 1991), and accelerated apoptosis is believed to underlie many neurodegenerative diseases, including Parkinson's disease (Barinaga, *Science* **281**: 1303-1304, 1998; Mochizuki *et al.*, *J. Neurol. Sci.* **137**: 120-123, 1996; and Oo *et al.*, *Neuroscience* **69**: 893-901, 1995). In living systems, apoptotic death can be initiated by a variety of external stimuli, and the biochemical nature of the intracellular apoptosis effectors is at least partially understood.

In a further embodiment, a composition of the invention is administered in

combination therapy with one or more additional drugs or prodrugs. The term "combination therapy" or "conjoint therapy" herein means a treatment regimen wherein the agent provided by the composition of the invention and a second agent are administered individually or together, sequentially or simultaneously, in such a way as to provide a beneficial effect from co-action of these therapeutic agents. Such beneficial effect can include, but is not limited to, pharmacokinetic or pharmacodynamic co-action of the therapeutic agents. Combination therapy can, for example, enable administration of a lower dose of one or both agents than would normally be administered during monotherapy, thus decreasing risk or incidence of adverse effects associated with higher doses. Alternatively, combination therapy can result in increased therapeutic effect at the normal dose of each agent in monotherapy.

Compositions of the invention can be especially suited to combination therapies, particularly where the second agent is one that is, or can be, administered once daily. There are significant advantages in patient convenience and compliance where both components of a combination therapy can be administered at the same time and with the same frequency. This is especially true in the case of geriatric patients or those suffering memory impairment.

When administered simultaneously, the two components of the combination therapy can be administered in separate dosage forms or in coformulation, *i.e.*, in a single dosage form, When administered sequentially or in separate dosage forms, the second agent can be administered by any suitable route and in any pharmaceutically acceptable dosage form, for example by a route and/or in a dosage form other than the present composition. In a preferred embodiment, both components of the combination therapy are formulated together in a single dosage form.

The second components of the subject combination therapy, *e.g.*, drugs useful for the treatment Parkinson's disease and other movement disorders, include L-dopa, selegiline, apomorphine and anticholinergics. L-dopa (levo-dihydroxy-phenylalanine) is a dopamine precursor which can cross the blood-brain barrier and be converted to dopamine in the brain. Unfortunately, L-dopa has a short half life in the body and it is typical after long use (*i.e.*, after about 4-5 years) for the effect of L-dopa to become sporadic and unpredictable, resulting in fluctuations in motor function, dyskinesias and psychiatric side effects. Additionally, L-dopa can cause B vitamin deficiencies to arise.

The gastrointestinal absorption of orally administered levodopa depends on the gastrointestinal transit rates as absorption occurs primarily in the proximal third of the intestine (duodenum/jejunum) and not in the stomach (Rivera-Calimlim *et al.* Europ. J. Clin.

Invest. 1, 1313-1320, 1971). Therefore a delayed release dosage form containing levodopa/carbidopa or levodopa/carbidopa/entacapone with pramipexole will allow the levodopa to be released in the target proximal intestine region and release levodopa is a sustained manner similar to enteral infusion of levodopa.

Thus in certain embodiments, the invention provides a pharmaceutical composition comprising pramipexole and levodopa (optionally also carbidopa or a prodrug thereof) for treating PD and other related movement disorders. The invention also provides methods of using such pharmaceutical compositions for treating PD and other related movement disorders. See Examples 86-89 of WO 2007/002516.

Selegiline (Deprenyl, Eldepryl) has been used as an alternative to L-dopa, and acts by reducing the breakdown of dopamine in the brain. Unfortunately, selegiline becomes ineffective after about nine months of use. Apomorphine, a dopamine receptor agonist, has been used to treat Parkinson's disease, although is causes severe vomiting when used on its own, as well as skin reactions, infection, drowsiness and some psychiatric side effects.

Systemically administered anticholinergic drugs (such as benzhexol and orphenedrine) have also been used to treat Parkinson's disease and act by reducing the amount of acetylcholine produced in the brain and thereby redress the dopamine/acetylcholine imbalance present in Parkinson's disease. Unfortunately, about 70% of patients taking systemically administered anticholinergics develop serious neuropsychiatric side effects, including hallucinations, as well as dyskinetic movements, and other effects resulting from wide anticholinergic distribution, including vision effects, difficulty swallowing, dry mouth, and urine retention. See *e.g.* Playfer, *Parkinson's Disease*, *Postgrad Med J* **73**: 257-264, 1997 and Nadeau, *Parkinson's Disease*, *J Am Ger Soc* **45**: 233-240, 1997.

Newer drug refinements and developments include direct-acting dopamine agonists, slow-release L-dopa formulations, inhibitors of the dopamine degrading enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase B (MAO-B), and dopamine transport blockers. These treatments enhance central dopaminergic neurotransmission during the early stages of Parkinson's disease, ameliorate symptoms associated with Parkinson's disease, and temporarily improve the quality of life. However, despite improvements in the use of L-dopa for treating Parkinson's disease, the benefits accorded by these dopaminergic therapies are temporary, and their efficacy declines with disease progression. In addition, these treatments are accompanied by severe adverse motor and mental effects, most notably dyskinesias at peak dose and "on-off" fluctuations in drug effectiveness (Poewe and Granata, in *Movement*

Disorders. Neurological Principles and Practice (Watts and Koller, eds) McGraw-Hill, New York, 1997; and Marsden and Parkes, *Lancet* 1: 345-349, 1977). No drug treatments are currently available that lessen the progressive pace of nigrostriatal degeneration, postpone the onset of illness, or that substantively slow disability (Shoulson, *supra*).

Other methods for the treatment of Parkinson's disease involve neurosurgical intervention, such as thalamotomy, pallidotomy, and deep brain stimulation. The thalamic outputs of the basal ganglia are an effective lesion target for the control of tremor (*i.e.*, thalamotomy). Thalamotomy destroys part of the thalamus, a brain region involved in movement control. Unilateral stereotactic thalamotomy has proven to be effective for controlling contralateral tremor and rigidity, but carries a risk of hemiparesis. Bilateral thalamotomy carries an increased risk of speech and swallowing disorders resulting.

Stereotactic pallidotomy, surgical ablation of part of the globus pallidus (a basal ganglia), has also be used with some success. Pallidotomy is performed by inserting a wire probe into the globus pallidus and heating the probe to destroy nearby tissue. Pallidotomy is most useful for the treatment of peak-dose diskinesias and for dystonia that occurs at the end of a dose.

Aside from surgical resection, deep brain stimulation, high frequency stimulating electrodes placed in the ventral intermedialis nucleus, has been found to suppress abnormal movements in some cases. A variety of techniques exist to permit precise location of a probe, including computed tomography and magnetic resonance imaging. Unfortunately, the akinesia, speech and gait disorder symptoms of Parkinson's disease are little helped by these surgical procedures, all of which result in destructive brain lesions. Despite the development of modem imaging and surgical techniques to improve the effectiveness of these neurosurgical interventions for the treatment of Parkinson's disease tremor symptoms, the use of neurosurgical therapies is not widely applicable. For example, thalamotomy does not alleviate the akinetic symptoms which are the major functional disability for many people suffering from Parkinson's disease (Marsden *et al.*, *Adv. Neurol.* **74**: 143-147, 1997).

Therapeutic methods aimed at controlling suspected causative factors associated with Parkinson's disease (*e.g.*, therapies which control oxidative stress and excitotoxicity) have also been developed. Clinical trials have shown that administration of antioxidative agents vitamin E and deprenyl provided little or no neuroprotective function (Shoulson *et al.*, *Ann. Neurol.* **43**: 318-325, 1998). Glutamate-receptor blockers and neuronal nitric oxide synthase (NOS) inhibitors have been proposed as therapies for Parkinson's disease; however, no

experimental results from human studies have yet been published (Rodriguez, *Ann. Neurol.* **44**: S175-S188, 1998).

The use of neurotrophic factors to stimulate neuronal repair, survival, and growth in Parkinson's disease has also been studied, particularly the use of glial cell line-derived neurotrophic factor (GDNF). Although GDNF protein protects some dopamine neurons from death, it is difficult to supply GDNF protein to the brain. Furthermore, the use of such protein therapies in general is problematic, since protein molecules show rapid *in vivo* degradation, are unable to penetrate the blood-brain barrier, and must be directly injected into the ventricles of the patient's brain (Palfi *et al.*, *Soc. Neurosci. Abstr.* **24**: 41, 1998; Hagg, *Exp. Neurol.* **149**: 183-192, 1998; and Dunnett and Bjorklund, *supra*). Other neurotrophic factors which may have therapeutic value have been proposed based on *in vitro* and animal model systems, including neurturin, basic fibroblast growth factor (bFGF), brain-derived neurotrophic factor (BDNF), neurotrophins 3 and 4/5, ciliary neurotrophic factor and transforming growth factor ß (TGF-ß). However, the effectiveness of these therapies in humans remains unknown. At present, no single chemical compound or peptide has been reported to completely protect dopamine neurons from death by tropic factor withdrawal or neurotoxin exposure.

Cell replacement therapies have also received much attention as potential methods for treating Parkinson's disease (Freed *et al.*, *Arch. Neurol.* **47**: 505-512, 1990; Freed *et al.*, *N. Engl. J. Med.* **327**: 1549-1555, 1992; Lindvall *et al.*, *Science* **247**: 574-577, 1990; Spencer *et al.*, *N. Engl. J. Med.* **327**: 1541-1548, 1992; Widner *et al.*, *N. Engl. J. Med.* **327**: 1556-1563, 1992; Lindvall, *NeuroReport* **8**: iii-x, 1997; Olanow *et al.*, *Adv. Neurol.* **74**: 249-269, 1997; and Lindvall, *Nature Biotechn.* **17**: 635-636, 1999). These neural grafting therapies use dopamine supplied from cells implanted into the striatum as a substitute for nigrostriatal dopaminergic neurons that have been lost due to neurodegeneration. Although animal models and preliminary human clinical studies have shown that cell replacement therapies may be useful in the treatment of Parkinson's disease, the failure of the transplanted neurons to survive in the striatum is a major impediment in the development of cell replacement therapies.

Various sources of dopaminergic neurons for use in the transplantation process have been tried in animal experiments, including the use of mesencephalic dopamine neurons obtained from human embryo cadavers, immature neuronal precursor cells (*i.e.*, neuronal stem cells), dopamine secreting non-neuronal cells, terminally differentiated teratocarcinoma-

derived neuronal cell lines (Dunnett and Bjorkland, *supra*), genetically modified cells (Raymon *et al.*, *Exp. Neurol.* **144**: 82-91, 1997; and Kang, *Mov. Dis.* **13**: 59-72, 1998), cells from cloned embryos (Zawada *et al.*, *Nature Medicine* **4**: 569-573, 1998) and xenogenic cells (Bjorklund *et al.*; *Nature* **298**: 652-654, 1982; Huffaker *et al.*, *Exp. Brain Res.* **77**: 329-336, 1989; Galpem *et al.*, *Exp. Neurol.* **140**: 1-13, 1996; Deacon *et al.*, *Nature Med.* **3**: 350-353, 1997; and Zawada *et al.*, *Nature Med.* **4**: 569-573, 1998). Nonetheless, in current grafting protocols, no more than 5-20% of the transplanted dopamine neurons survive.

Additional therapies are also available, such as physical therapy, occupational therapy, or speech / language therapy. Exercise, diet, nutrition, patient/caregiver education, and psychosocial interventions have also been shown to have a positive effect on the mental and/or physical state of a person suffering from Parkinson's disease.

Various methods of evaluating Parkinson's disease in a patient include Hoehn and Yahr Staging of Parkinson's Disease, Unified Parkinson Disease Rating Scale (UPDRS), and Schwab and England Activities of Daily Living Scale.

A person suffering from Parkinson's disease should avoid contraindicated and potentially contraindicated drugs such as antipsychotic drugs, Haloperidol (Haldol), Perphenazine (Trilafon), Chlorpromazine (Thorazine), Trifluoperazine (Stelazine), Flufenazine (Prolixin, Permitil) Thiothixene (Navane), Thioridazine (Mellaril); antidepressant drug, combination of Perphenazine and Amitriptyline (Triavil); anti-vomiting drugs, Prochlorperazine (Compazine), Metoclopramide (Reglan, Maxeran), Thiethylperazine (Torecan), Reserpine (Serpasil), Tetrabenazine (Nitoman); blood pressure drug, Alpha-methyldopa (Aldomet); anti-seizure drug, Phenytoin (Dilantin); mood stabilizing drug, lithium; and anti-anxiety drug, Buspirone (Buspar).

IV. *Exemplary Levodopa/Carbidopa Pharmaceutical Compositions for First Immediate-Release Portion, Second Substantial Zero-order Release Portion, and Second IR or Substantially Ascending Release Portion*

Certain embodiments of the invention provides a pharmaceutical preparation comprising an oral dosage formulation in a therapeutically effective amount sufficient to treat movement disorder (*e.g.*, Parkinson's disease or another movement disorder) in a patient, wherein the dosage formulation, when administered to the patient, provides a treatment regimen characterized by a rapid (immediate) release portion that quickly (*e.g.*, in less than about 2 hours, *e.g.*, in less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45

min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*, after administration) boosts effective levodopa concentration to a therapeutically effective level, followed by a substantially sustained dose (zero-order release dose) over at least about 2 hours, 4 hours, 6 hours, 8, hours, 12 hours, 16 hours, 20 hours, or at least about 24 hours. Optionally, a substantially ascending portion, such as a second IR portion, is also provided subsequent to the second zero-order release portion to ensure a rapid drop at the end of the therapeutic regimen cycle (*e.g.*, at day end, or before the patient goes to bed).

Certain embodiments of the invention provide a pharmaceutical preparation / dosage formulation provided in the form of a transdermal patch and formulated for sustained release formulation, in a therapeutically effective amount sufficient to treat a movement disorder (*e.g.,* Parkinson's disease and related movement disorders) in a patient, wherein the dosage formulation, when administered (provided as a patch) to the patient, provides a substantially sustained dose over at least about 2 hours, 4 hours, 6 hours, 8, hours, 12 hours, 20 hours, or at least about 24 hours.

For the treatment of Parkinson's disease, the first IR portion preferably contains a relatively high ratio of decarboxylase inhibitor (*e.g.*, carbidopa) / levodopa. In case of carbidopa / levodopa, the ratio is preferably > 1:4, or 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1 or higher. The first IR is formulated to quickly release the compositions such that an effective therapeutic concentration of levodopa is reached in less than about 2 hours (*e.g.*, in less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administration.

In certain embodiments, carbidopa may be administered before release of the first IR portion of levodopa, thereby more effectively inhibiting peripheral decarboxylase activity and maximizing the efficacy of the levodopa in the first IR portion. For example, there may be a layer comprising carbidopa that is released prior to the first IR portion, carbidopa in the IR portion may be formulated to release faster than the levodopa in the IR portion (*e.g.*, higher release ratio of carbidopa/levodopa), or a bioadhesive layer comprising a high proportion of carbidopa that at least partially undergoes immediate release may be present. Alternatively, the carbidopa may be administered as a separate formulation, *e.g.*, together with a levodopa composition coated with a delayed release coating.

The second sustained release (zero-order release) portion may contain a single

uniform composition (*e.g.*, with a uniform ratio of carbidopa / levodopa throughout). Alternatively, the second substantially zero order release portion may have a gradient of carbidopa / levodopa ratio from start to finish. For example, the ratio may approach 1:4 at the beginning of the second portion, but drop continuously or discontinuously to, for example, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, or 1:20, *etc.* If there is a discontinuous drop, the second portion may comprise several sub-portions, each possibly having a unique carbidopa / levodopa ratio.

The rapidly ascending release portion (such as the second IR portion) may contain no carbidopa, or fairly low ratio of carbidopa / levodopa, such that a rapid drop in effective levodopa concentration may be achieved, thus avoiding the long-tail effect that interferes with patient sleeping or rest.

In addition to carbidopa / levodopa, the portions of the subject dosage forms may additionally comprise compositions other than pharmaceutically acceptable carriers, exipients, or diluents, *etc.* (see details below). Such additional compositions may comprise a dopamine transporter inhibitor to be released with a delay. Such additional compositions may also comprise other pharmaceutical compositions useful for treating Parkinson's disease (*e.g.*, in conjoint therapy).

In either oral or patch form, the above-described dosage preparation can be one wherein the pharmaceutical composition is formulated in a multiplicity of (sub-)portions or polymeric layers. For example, in certain embodiments, the second sustained release portion may comprise a multiplicity of layers such that the preparation optionally delivers to the patient a sustained release portion with varying ratios of decarboxylase / levodopa over time, even when the amount of released levodopa remains largely constant. Thus, the subject pharmaceutical composition can be provided in an initial portion (*e.g.*, for immediate-release or IR), followed by a second portion (*e.g.*, substantially zero-order sustained release or SR, optionally with more than one sub-portions or a continuously changing ratio of inhibitor / levodopa), and a final portion (*e.g.*, an additional immediate-release portion), whereby the preparation delivers the initial dose, the second dose, then a final dose over time.

In other embodiments, the dose preparation can also be a plurality of beads, each bead including a subject pharmaceutical composition independently having a dissolution profile, which plurality of beads is a variegated population with respect to ratios of the pharmaceutical composition and/or dissolution profile, so as deliver, upon administration, the immediate, sustained, and increasing dose of the subject pharmaceutical composition. Several

exemplary embodiments of the dosage forms are described in more details below.

In still other embodiments, the dose preparation is generated such that the subject pharmaceutical composition is (i) contained within a nonabsorbable shell that releases the drug at a controlled rate, and (ii) formulated in at least two different dissolution profiles.

In certain embodiments, the dosage formulations of the present invention have a side-effect therapeutic index, (SeD_{50}/ED_{50}), such as with respect to the movement disorder, that is at least 2 times greater than the same amount of drug provided in immediate release form, and more preferably at least 5, 10 or even 100 times greater.

In certain embodiments, the subject packages, preparations, pharmaceutical compositions, and methods for the treatment of movement disorders further comprise one or more therapeutic agents for treating Parkinson's disease selected from a dopamine precursor, such as L-dopa; a dopaminergic agent, such as Levodopa-carbidopa (SINEMET®, SINEMET CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a dopaminergic and anti-cholinergic agent, such as amantadine (SYMMETRYL®, SYMADINE®); an anti-cholinergic agent, such as trihexyphenidyl (ARTANE®), benztropine (COGENTIN®), ethopropazine (PARSITAN®), or procyclidine (KEMADRIN®); a dopamine agonist, such as apomorphine, bromocriptine (PARLODEL®), cabergoline (DOSTINEX®), lisuride (DOPERGINE®), pergolide (PERMAX®), pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a MAO-B (monoamine oxidase B) inhibitor, such as selegiline or deprenyl (ATAPRYL®, CARBEX®, ELDEPRYL®); a COMT (catechol O-methyltransferase) inhibitor, such as CGP-28014, tolcapone (TASMAR®) or entacapone (COMTAN®); or other therapeutic agents, such as baclofen (LIORESAL®), domperidone (MOTILIUM®), fludrocortisone (FLORINEF®), midodrine (AMATINE®), oxybutynin (DITROPAN®), propranolol (INDERAL®, INDERAL-LA®), clonazepam (RIVOTRIL®), or yohimbine.

The subject treatment may also be used either in conjoint therapy with, or additionally include one or more other pharmaceutical compositions, such as the ones described below.

For example, US20030045539 (incorporated herein by reference) discloses a combination treatment of cabergoline and pramipexole provided concurrently to a patient suffering from various central nervous system diseases, and in particular for the treatment of Parkinson's Disease (PD). The initial dose of cabergoline is administered to the patient at a dose of 0.5 to 1 mg/patient/day and is adjusted upward at weekly intervals to a therapeutic dosage of 2, 4, 6, 8 or 10 mg/patient/day and where the initial dose of pramipexole is started at 0.375 mg/patient/day and is adjusted upward every 5 to 7 days to a therapeutic dosage of 3,

4, 5, 6, or 7 mg/patient/day. At least one portion of the subject pharmaceutical composition may additional comprise cabergoline and pramipexole for treating Parkinson's disease.

US20040166159 (incorporated herein by reference) discloses a pharmaceutical dosage forms having immediate and controlled release properties that contain an aromatic amino acid decarboxylase (AAAD) inhibitor (such as carbidopa), levodopa, and optionally a catechol-O-methyltransferase (COMT) inhibitor, for the treatment of medical conditions associated with reduced dopamine levels in a patient's brain. The dosage form may comprise up to about 1000 mg, or about 20-500 mg, about 50-500 mg, or about 100-200 mg of COMT inhibitor. The COMT inhibitor may be contained only within the immediate release component, or only within the sustained release component, or both. The COMT inhibitor may be CGP-28014, entacapone, or tolcapone. The dosage form may further comprise one or more drugs such as anti-cholinergics, beta 2-agonists, cyclooxygenase-2 (COX-2) inhibitors, dopamine receptor agonists, monoamine oxidase (MAO) inhibitors, opiate delta receptor agonists, opiate delta receptor antagonists, and N-methyl-D-aspartate (NMDA) antagonists. The dosage form may further comprise one or more drugs selected from albuterol, alpha-lipoic acid, amantadine, andropinirole, apomorphine, baclofen, biperiden, benztropine, bromocriptine, budipine, cabergoline, clozapine, deprenyl, dextromethorphan, dihydroergokryptine, dihydrolipoic acid, eliprodil, eptastigmine, ergoline, formoterol, galanthamine, lazabemide, lysuride, mazindol, memantine, mofegiline, orphenadrine, pergolide, pirbuterol, pramipexole, propentofylline, procyclidine, rasagiline, remacemide, riluzole, rimantadine, ropinirole, salmeterol, selegiline, spheramine, terguride, and trihexyphenidyl.

Similarly, other movement disorders may also be treated with similar methods and suitable pharmaceutical compositions, such as the ones described below.

For example, in certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating dystonia selected from an anti-cholinergic agent, such as trihexyphenidyl (ARTANE®), benztropine (COGENTIN®), ethoproprazine (PARSITAN®), or procyclidine (KEMADRIN®); a dopaminergic agent, such as Levodopa-carbidopa (SINEMET®, SINEMET CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a muscle relaxant, such as baclofen (LIORESAL®); a sedative, such as Clonazepam (RIVOTRIL®); an anticonvulsant agent, such as carbamazepine (TEGRETOL®); a dopamine reuptake inhibitor, such as tetrabenazine (NITOMAN®); or a dopamine blocker, such as haloperidol (HALDOL®).

In certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating tremor selected from a β-blocker, such as propranolol (INDERAL®, INDERAL-LA®); an anticonvulsant agent, such as primidone (MYSOLINE®); or a carbonic anhydrase inhibitor, such as acetalzolamide (DIAMOX®) or methazolamide (NEPTAZANE®).

In certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating myoclonus selected from a sedative, such as clonazepam (RIVOTRIL®); or an anticonvulsant agent, such as valproic acid (EPIVAL®).

In certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating chorea selected from a dopamine blocker, such as haloperidol (HALDOL®); or a dopamine reuptake inhibitor, such as tetrabenazine (NITOMAN®).

In certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating restless leg syndrome selected from a dopaminergic, such as Levodopa-carbidopa (SINEMET®, SINEMET CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a sedative, such as clonazepam (RIVOTRIL®); a dopamine agonists, such as bromocriptine (PARLODEL®), pergolide (PERMAX®), pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a narcotic agent, such as codeine (TYLENOL # 3®); or a GABAergic agent, such as gabapentin (NEURONTIN®).

In certain embodiments of the subject packages, preparations, compositions, and methods for the treatment of movement disorders, the invention further comprises one or more therapeutic agents for treating tics selected from a sedative, such as clonazepam (RIVOTRIL®); an alpha antagonist, such as clonidine (CATAPRESS®); a dopamine reuptake inhibitor, such as tetrabenazine (NITOMAN®); or a dopamine blocker, such as haloperidol (HALDOL®) or perphenazine.

In certain embodiments, the present invention provides pharmaceutical preparations comprising, as an active ingredient, an enantiomerically enriched preparation of R-(-) amphetamine or a derivative thereof. The subject amphetamine compound is formulated in an amount sufficient to treat or prevent a movement disorder in an animal.

Still another embodiment of the invention relates to the use of enantiomerically

enriched preparations of amphetamine compounds for lessening the severity or prophylactically preventing the occurrence of movement disorders in an animal, and thus, altering the mental or physical state of the animal. The compounds of the present invention may also be useful for treating and/or preventing memory impairment, *e.g.*, due to a movement disorder.

It should be noted that levodopa and carbidopa of the subject pharmaceutical composition can be replaced in whole or in part in this invention with appropriate prodrugs, stereoisomers, acceptable salts, hydrates, solvates, *etc.* Levodopa prodrugs include any pharmaceutically suitable ester of levodopa such as, but not limited to, the methyl, ethyl, or propyl esters of levodopa, or combinations thereof. Levodopa may be in the form of (−)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid, 3-hydroxy-L-tyrosine ethyl ester, phenylglycine, or a mixture thereof. The following specific examples describe levodopa prodrugs and carbidopa prodrugs, as well as additional compositions (such as fillers, organic acids, metals, metal chelators, *etc.*) that might constitute useful supplements to the backbone levodopa / carbidopa composition. These compositions may be used as the subject pharmaceutical composition.

For example, US20020151589A1 (incorporated herein by reference) describes a dispersible pharmaceutical composition comprising a therapeutically effective amount of L-DOPA ethyl ester, a therapeutically effective amount of a decarboxylase inhibitor, a filler, a disintegrant, and a lubricant, and a method of preparing the pharmaceutical composition described herein. The filler may be corn starch, glucose, various natural gums, methylcellulose, carboxymethylcellulose, microcrystalline cellulose, calcium phosphate, calcium carbonate, calcium sulfate kaolin, sodium chloride, powdered cellulose, sucrose, mannitol and starch, preferably microcrystalline cellulose (with a moisture content of up to about 1.5%, or up to about 5.0%). The decarboxylase inhibitor may be carbidopa (with a moisture content of, for example, between 5.0-10.0%, preferably 7.5%) or benserazide. The disintegrant may be kaolin, starch, powdered sugar, sodium starch glycolate, crosscarmelose sodium, carboxymethyl cellulose, microcrystalline cellulose and sodium alginate, preferably pregelatinized starch (with a moisture content of up to about 5, 7, 12, or 14%). The lubricant may be talc, sodium stearyl fumarate, magnesium stearate, calcium stearate, hydrogenated castor oil, hydrogenated soybean oil, and polyethylene glycol, preferably magnesium stearate. The excipient may be a binding agent such as sorbitol, glucose, xylitol, and mannitol. The composition may further comprise an antioxidant such as tocopherol, sodium metabisulphite,

butylated hydroxytoluene, butylated hydroxyanisole, ascorbic acid and sodium ascorbate, preferably sodium metabisulphite. Various weight percentages and amounts per dose are also disclosed, and incorporated herein by reference. Such levodopa ethyl ester and the other described components may be used as the levodopa composition of the invention.

In another example, US20020192290A1 (incorporated herein by reference) discloses a pharmaceutical composition comprising a therapeutically effective amount of levodopa and of carbidopa, dispersed in a hydrophilic matrix, the composition further comprising an organic acid. The process for preparing the composition, comprising granulation, in particular in a fluidized bed, of the various components and compression of the granules obtained, is also disclosed. The organic acid may be fumaric acid, citric acid, ascorbic acid, maleic acid, glutamic acid, malonic acid and oxalic acid. The organic acid may represent from 0.2% to 20% by weight relative to the weight of the composition. The hydrophilic matrix (such as hydroxypropylmethyl cellulose) may represent from 10% to 80% by weight relative to the weight of the composition. The hydrophilic matrix may also comprise an insoluble substance, such as microcrystalline cellulose.

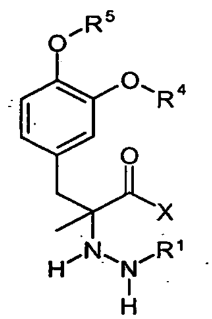
US20040028613A1 (incorporated herein by reference) discloses formulation useful for enhancing peak concentrations in CNS tissues or fluids and for treating, for example, Parkinson's disease, comprises dopamine agonist and at least one delivery enhancing agent. The dopamine receptor agonist may be apomorphine or a pharmaceutically acceptable salt or derivative thereof, and is administered to the subject in an effective dose of between about 0.25 and 2.0 mg. The delivery-enhancing agent(s) is/are selected from: (a) an aggregation inhibitory agent; (b) a charge modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (ii) a phospholipid additive, mixed micelle, liposome, or carrier, (iii) an alcohol, (iv) an enamine, (v) an NO donor compound, (vi) a long-chain amphipathic molecule (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid (x) a clyclodextrin or beta-cyclodextrin derivative, (xi) a medium-chain fatty acid, (xii) a chelating agent, (xiii) an amino acid or salt thereof, (xiv) an N-acetylamino acid or salt thereof, (xv) an enzyme degradative to a selected membrane component, (ix) an inhibitor of fatty acid synthesis, or (x) an inhibitor of cholesterol synthesis; or (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a

selective transport-enhancing agent; and (k) a stabilizing delivery vehicle, carrier, support or complex-forming species with which the dopamine receptor agonist is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the dopamine receptor agonist for enhanced mucosal delivery, wherein the formulation of the dopamine receptor agonist with the one or more delivery-enhancing agents provides for increased bioavailability of the dopamine receptor agonist in a central nervous system tissue or fluid of the subject. The delivery-enhancing agent(s) may also be selected from citric acid, sodium citrate, propylene glycol, glycerin, L-ascorbic acid, sodium metabisulfite, edetate disodium, benzalkonium chloride, sodium hydroxide and mixtures thereof.

US20050070608 (incorporated herein by reference) discloses a composition useful for treating dopamine disorders, *e.g.*, Parkinson's disease, comprises levodopa, carbidopa, acid and optionally metal chelator or thioether compound. The metal chelator may be EDTA, or deferoxamine mesylate. The EDTA may be in the form of a salt of a free base, and/or at a concentration of at least about 0.01 mg/ml. The acid may be a carboxylic acid, a mineral acid, citric acid, tartaric acid, ascorbic acid, dehydroascorbic acid, acetic acid (ethanoic acid), formic acid (methanoic acid), butyric acid (butanoic acid), benzoic acid, malic acid, propionic acid, epoxysuccinic acid, muconic acid, furanacrylic acid, citramalic acid, capric acid, stearic acid, caproic acid, malonic acid, succinic acid, diethylacetic acid, methylbutryic acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, and sulfuric acid, but preferably not ascorbic acid. The composition does not contain sugar. The composition may be a liquid. Preferably, less than 10%, or 5% of the carbidopa has degraded at 25°C after 7 days, or less than 10% of the carbidopa has degraded at 25°C after 30 days, or less than 5% of the carbidopa has degraded at 25°C after 4 days. The composition may further comprise an artificial sweetener, such as aspartame. The composition may further comprise a preservative, such as sodium benzoate. The composition may be clear or translucent.

US20040167216 and its PCT counterpart WO04/052841A1 (both incorporated herein by reference) discloses prodrugs of carbidopa, derivatives of carbidopa prodrugs, methods of making and using such prodrugs and derivatives thereof, and compositions of such prodrugs and derivatives thereof. All such prodrugs may be used as carbidopa substitutes in the instant invention.

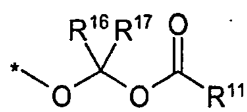
For example, In certain embodiments, the prodrug is compound of Formula (I):



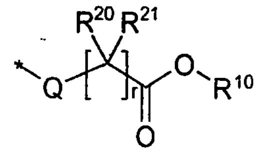
(I)

a stereoisomer thereof, an enantiomer thereof, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate of any of the foregoing, wherein:

X is selected from $-OR^{10}$ and moieties of Formulae (II) and (III):

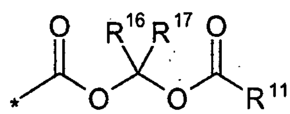


(II)



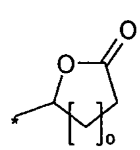
(III)

where: r is an integer from 1 to 6; Q is O or $-NR^{15}$; $-R^1$ is selected from hydrogen and a moiety comprising Formula (IX):

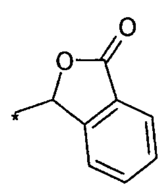


(IX)

R^4 and R^5 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroalkyl, substituted heteroalkyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, - $C(O)OR^{27}$, $-C(O)R^{27}$, $-(CR^{16}R^{17})OC(O)R^{11}$ and moieties of Formulae (XVII) and (XVIII):



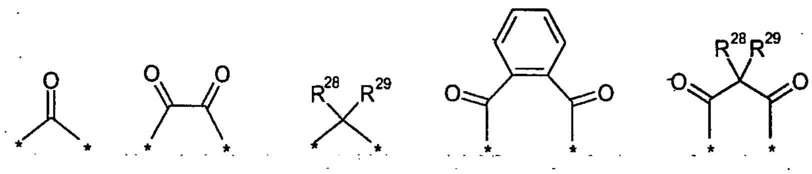
(XVII)



(XVIII)

wherein o is 1-3, and the cycloheteroalkyl rings in (XVII) and (XVTII) are optionally

substituted with one or more groups selected from halo, CN, NO_2, OH, C_{1-6} alkyl, and C_{1-6} alkoxy; or R^4 and R^5 together form a structure selected from Formulae (XII) to (XVI):



(XII) (XIII) (XIV) (XV) (XVI)

wherein the aryl ring in Formula (XV) is optionally substituted with one or more groups selected from halo, CN, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and $-CO_2R^{31}$;

R^{10} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{11} is selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^{11} and either R^{16} or R^{17}, together with the atoms to which R^{11}, and either R^{16} or R^{17} are attached, form a cycloheteroalkyl or substituted cycloheteroalkyl ring, optionally to which is fused an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{15} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, and substituted arylalkyl;

R^{16} and R^{17} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, carbamoyl, substituted carbomoyl, cycloalkyl, substituted cycloalkyl, cycloalkoxycarbonyl, substituted cycloalkoxycarbonyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl or optionally, R^{16} and R^{17} together with the carbon atom to which R^{16} and R^{17} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring; each R^{20} and R^{21} is independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, alkylamino, substituted

alkylarnino, alklysulfinyl, substituted alkylsulfinyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy, and substituted heteroaryloxy, or optionally, when r is 1, then R^{20} and R^{21} together with the carbon atom to which R^{20} and R^{21} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring, or optionally when R^{20} and R^{15} are present and are attached to adjacent atoms then R^{15} and R^{20} together with the atoms to which R^{15} and R^{20} are attached form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{27} is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{28} and R^{29} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroalkyl, and substituted heteroalkyl;

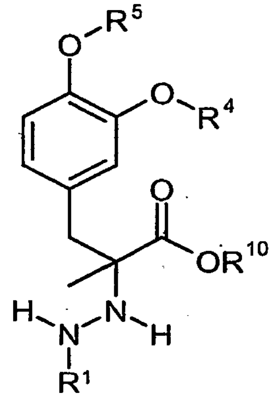
and R^{31} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

with the provisos that

when X is $-OR^{10}$, R^1 is hydrogen, and R^4 and R^5 are independently selected from hydrogen and C_{1-19} alkyl, C_{1-19} aryl or C_{1-19} arylalkyl, then R^{10} is not hydrogen or C_{1-6} alkyl; and

none of R^1, R^4, R^5, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{27}, R^{28}, R^{29}, and R^{31} comprise a bile acid moiety.

In another embodiment, the prodrug is a compound of Formula (Ia):



(Ia)

a stereoisomer thereof, an enantiomer thereof, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate of any of the foregoing, wherein:

R^1 is selected from hydrogen and the structure of Formula (IX): see above;

R^4 and R^5 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroalkyl, substituted heteroalkyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, $-C(O)OR^{27}$, $-C(O)R^{27}$, $-(CR^{16}R^{17})OC(O)R$ and moieties of Formulae (XVII) and (XVIII): see above;

wherein o is 1-3, and the cycloheteroalkyl rings in (XVII) and (XVIII) are optionally substituted with one or more groups selected from halo, CN, NO_2, OH, C_{1-6} alkyl, and C_{1-6} alkoxy;

or R^4 and R^5 together form a structure selected from Formulae (XII) to (XVI) (see above);

wherein the aryl ring in Formula (XV) is optionally substituted with one or more groups selected from halo, CN, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and $-CO_2R^{31}$;

R^{10} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{11} is selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or

optionally, R^{11} and either R^{16} or R^{17}, together with the atoms to which R^{11}, and either R^{16} or R^{17} are attached, form a first cycloheteroalkyl or substituted cycloheteroalkyl ring, to which an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring is optionally fused to said first cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{16} or R^{17} are independently selected from hydrogen, alkyl, substituted alkyd, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroarylalkyl, and substituted heteroarylalkyl or optionally, R^{16} or R^{17} together with the carbon atoms to which R^{16} or R^{17} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{27} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{28} and R^{29} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroalkyl, and substituted heteroalkyl; and

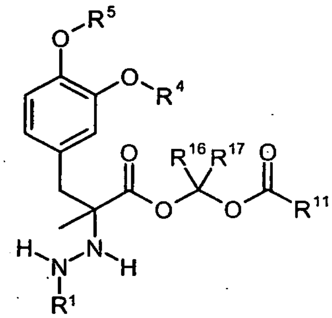
R^{31} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

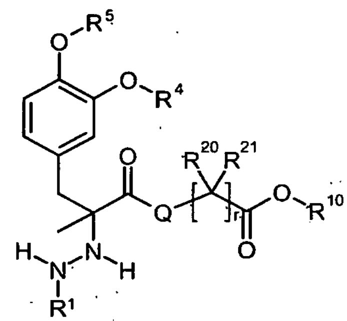
with the provisos that

when R^1 hydrogen, and R^4 and R^5 are independently selected front hydrogen, C_{1-19} alkyl, C1-19 aryl, or C_{1-19} arylalkyl, then R^{10} is not hydrogen or C_{1-6} alkyl; and

none of R^1, R^4, R^5, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{27}, R^{28}, R^{29}, and R^{31} comprise a bile acid moiety.

In yet another embodiment, the prodrug is a compound of Formulae (Ib) or (Ic):


(Ib)


(Ic)

a stereoisomer thereof, an enantiomer thereof, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate of any of the foregoing, wherein:

Q is O or $-NR^{15}$;

r is an integer from 1 to 6;

R is selected from hydrogen and a moiety comprising Formula (IX) (see above);

R^4 and R^5 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroalkyl, substituted heteroalkyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, $-C(O)OR^{27}$, $-C(O)R^{27}$, $-(CR^{16}R^{17})OC(O)R^{11}$, and moieties of Formulae (XVII) and (XVIII) (see above);

wherein o is 1-3, and the cycloheteroalkyl rings in (XVII) and (XVIII) are optionally substituted with one or more groups selected from halo, CN, NO_2, OH, C_{1-6} alkyl, and C_{1-6} alkoxy;

or R^4 and R^5 together form a structure selected from Formulae (XII) to (XVI) (see above);

wherein the aryl ring in Formula (XV) is optionally substituted with one or more groups selected from halo, CN, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and $-CO_2R^{31}$;

R^{10} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{11} is selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, cycloheteroalkyl, substituted cycloheteroalkyl,

heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^{11} and either R^{16} or R^{17}, together with the atoms to which R^{11}, R^{16} and R^{17} are attached, form a cycloheteroalkyl or substituted cycloheteroalkyl ring, to which an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring is optionally fused to said cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{15} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, and substituted arylalkyl;

R^{16} and R^{17} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroarylalkyl, and substituted heteroarylalkyl or optionally, R^{16} and R^{17} together with the carbon atoms to which R^{16} and R^{17} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

each R^{20} and R^{21} is independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, alkylamino, substituted alkylamino, alklysulfinyl, substituted alkylsulfnyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy, and substituted heteroaryloxy, or optionally, when r is 1, then R^{20} and R^{21} together with the carbon atom to which R^{20} and R^{21} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring, or optionally when R^{20} and R^{15} are present and are attached to adjacent atoms then R^{20} and R^{15} together with the atoms to which R^{20} and R^{15} are attached form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{27} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{28} and R^{29} are independently selected from hydrogen, alkyl, substituted alkyl,

alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroalkyl, and substituted heteroalkyl;

and R^{31} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

with the proviso that none of R^1, R^4, R^5, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{27}, R^{28}, R^{29}, and R^{31} comprise a bile acid moiety.

V. *Other Exemplary Levodopa/Carbidopa Dosage Forms*

Many dosage forms in the art may be readily adapted for use in the instant invention according to the general teaching of the invention. The following describe certain levodopa ethyl esters or derivatives thereof, which may be used in the instant invention.

US20030152628 (incorporated herein by reference) discloses a tablet which comprises an inner core formulated for controlled release consisting essentially of a mixture of levodopa ethyl ester or a derivative or a pharmaceutically acceptable salt thereof, a carrier and an inner core excipient component; and an outer layer encapsulating the inner core and formulated for immediate release comprising a mixture of a decarboxylase inhibitor and levodopa ethyl ester or a derivative or a pharmaceutically acceptable salt thereof.

US20030147957 (incorporated herein by reference) discloses a tablet which comprises: an inner core formulated for controlled release comprising a mixture of (a) a granulated admixture of a decarboxylase inhibitor and a surfactant, and (b) levodopa ethyl ester or a derivative or a pharmaceutically acceptable salt thereof; and an outer layer encapsulating the inner core and formulated for immediate release comprising a mixture of a granulated decarboxylase inhibitor and levodopa ethyl ester or a derivative or a pharmaceutically acceptable salt thereof. It also provides methods of manufacturing such tablets.

US20040234608 (incorporated herein by reference) discloses a pharmaceutical composition for use in a dosage form for oral administration to a patient. The composition expands upon contact with gastric fluid and promotes retention of the dosage form in the patient's stomach for a prolonged period of time. The application further provides pharmaceutical dosage forms containing an active ingredient, and the pharmaceutical composition. The forms are adapted for immediate or controlled release of the active

ingredient. The dosage forms may be used advantageously in the treatment of Parkinson's disease with levodopa and hyperactivity and attention deficit disorder with methylphenidate. The composition comprises a hydrogel, a superdisintegrant and tannic acid wherein the volume of the composition increases about three fold within about 15 minutes of contacting gastric fluid. Its volume increases about 5-8 fold within about fifteen minutes of contacting gastric fluid, or increases about 3 fold within about five minutes of contacting gastric fluid. The hydrogel may comprise hydroxypropyl methylcellulose, and may further comprise hydroxypropyl cellulose, preferably in a weight ratio of from about 1:3 to about 5:3. The hydrogel may further comprise a cross-linked polyacrylate, such as a polyacrylic acid polymer crosslinked with allyl sucrose. The superdisintegrant may be selected from cross-linked carboxymethylcellulose sodium, sodium starch glycolate and cross-linked polyvinylpyrrolidone, preferably cross-linked carboxymethylcellulose sodium or sodium starch glycolate. The tannic acid may be present in an amount of from about 2 weight percent to about 12 weight percent of the total weight of hydrogel, superdisintegrant and tannic acid, exclusive of other excipients that may be present.

US20040180086 (incorporated herein by reference) discloses gastro-retentive dosage forms for prolonged delivery of levodopa and carbidopa / levodopa combinations. The dosage forms comprise a tablet containing the active ingredient and a gas-generating agent sealed within an expandable, hydrophilic, water-permeable and substantially gas-impermeable membrane. Upon contact with gastric fluid, the membrane expands as a result of the release of gas from the gas-generating agent in the tablet. The expanded membrane is retained in the stomach for a prolonged period of time up to 24 hours or more during which period the active ingredient is released from the tablet providing delivery of levodopa to the site of optimum absorption in the upper small intestine. For example, the application discloses a gastro-retentive dosage form of levodopa for oral administration to a patient in need thereof, the dosage form comprising (a) a tablet comprising a therapeutically effective amount of levodopa, a binder, and a pharmaceutically-acceptable gas-generating agent capable of releasing carbon dioxide upon contact with gastric juice, and (b) an expandable, hydrophilic, water-permeable and substantially gas-impermeable, membrane surrounding the tablet, wherein the membrane expands as a result of the release of carbon dioxide from the gas-generating agent upon contact with the gastric juice, whereby the dosage form becomes too large to pass into the patient's pyloric sphincter. The dosage form may further comprise a covering (*e.g.*, a dry-fill capsule) for containing the dosage form, wherein the covering

disintegrates upon contact with gastric fluid. The membrane may comprise polyvinyl alcohol. The gas-generating agent may be sodium bicarbonate, sodium carbonate, sodium glycine carbonate, potassium carbonate, calcium carbonate, magnesium carbonate or mixtures thereof. The binder may be a polyoxyethylene stearate, a poloxamer, a polyethylene glycol, a glycerol palmitostearate, a glyceryl monostearate, a methylcellulose or a polyvinyl pyrrolidone, such as Myrj 52, Lutrol F68, PEG 3350, a methylcellulose or a polyvinyl pyrrolidone.

Other exemplary dosage forms that may be adapted according to the teachings of the instant invention include US20030228360A1 and US20040052843.

VI. *Exemplary Delivery Devices*

Various amounts of the subject drugs or pharmaceutical compositions can be included in tablets and drug eluting devices of the invention. Such tablets and drug eluting devices typically contain at least 1 mg of a drug / pharmaceutical composition. These tablets and drug eluting devices can also contain at least 2 mg, at least 5 mg, at least 10 mg, at least 25 mg, at least 50 mg, at least 100 mg, at least 500 mg or at least 1000 mg of a drug / pharmaceutical composition.

Any of the devices discussed below can be used to administer carbidopa, levodopa, or combinations of these drugs as discussed above, or they can be used to deliver any other drug desired to be administered, *e.g.*, to treat any medical condition or disease state, or for any therapeutic or diagnostic purpose. In general, drugs / pharmaceutical compositions suitable for use herein can be small organic molecules (*e.g.*, non-polymeric molecules having a molecular weight of 2000 amu or less, such as 1000 amu or less), peptides or polypeptides and nucleic acids.

More than one type of drug can be present in a tablet or a drug eluting device of the invention. The drugs can be evenly distributed throughout a medicament or can be heterogeneously distributed in a medicament, such that one drug is fully or partially released before a second drug. See different embodiments of the drug devices and/or layering in other parts of this specification.

Dosage forms of the invention typically weigh at least 5 mg. Dosage forms (such as the various shell designs of the invention) can also weigh at least 10 mg, at least 15 mg, at least 25 mg, at least 50 mg, at least 100 mg, at least 500 mg or at least 1000 mg.

Dosage forms of the invention typically measure at least 2 mm in one direction. For

example, dosage forms can measure at least 5 mm, at least 10 mm, at least 15 mm or at least 20 mm in one direction. Typically, the diameter of the dosage forms is 2 to 40 mm, preferably 10 to 30 mm such as 20 to 26 mm. Mini-tablets have a diameter of 2 mm to about 5 mm. Such dosage forms can measure at least 2 mm, at least 5 mm, at least 10 mm, at least 15 mm or least 20 mm in a second direction and, optionally, a third direction. Preferably, the dosage form is of a size that facilitates swallowing by a subject.

The volume of a typical dosage form of the invention is at least 0.008 mL, at least 0.01 mL, at least 0.05 mL, at least 0.1 mL, at least 0.125 mL, at least 0.2 mL, at least 0.3 mL, at least 0.4 mL or at least 0.5 mL.

To produce a dosage form that can release at least two or three drugs at two or three different rates, and with preprogrammed delays, special dosage forms are used. For example, in the embodiments of the invention wherein levodopa, carbidopa, and the transport inhibitors are designed to be released concomitantly, the drugs may be formulated as bilayer (or other multilayer) tablets or shells (*e.g.*, stacked layer of cakes, each may represent an independent formulation). Alternatively, levodopa and carbidopa may be formulated as a tablet within a tablet or bead (not limited to two nested layers). The outer tablet may contain a levodopa / carbidopa combination designed to be released together either as immediate release delivery patterns or as a sustained release delivery. The inner tablet / bead may be formulated to release after the outer tablet / bead has released the formulations. Optionally, the inner tablet(s) / bead(s) may be formulated with a coating layer to help achieve the desired delay in time.

In certain embodiments, the drugs may be formulated into a core tablet held in a recessed fashion within an annular ring of drug material. Such a dosage form is described in U.S. patent application Ser. No. 10/419,536 entitled "Dosage Form with a Core Tablet of Active Ingredient Sheathed in a Compressed Angular Body of Powder or Granular Material, and Process and Tooling for Producing It," filed on Apr. 21, 2003 and Ser. No. 10/379,338 entitled "Controlled Release Dosage Forms," filed on Mar. 3, 2003 and are incorporated herein by reference. The outer annular ring is formulated with the levodopa and decarboxylase enzyme inhibitor and formulated for either immediate release or sustained release delivery for the desired time. The inner core(s) of the dosage form contain the dopamine transport inhibitor to be released after a delay which may be formulated for the desired release profile.

Other embodiments of the invention use the dosage form described in U.S. patent

application Ser. No. 10/191,298 entitled "Drug Delivery System for Zero-order, Zero-Order Biphasic, Ascending or Descending Drug Delivery," filed on Jul. 10, 2002, incorporated herein by reference. The dopamine transport inhibitor may be formulated in the tablet mantle and released at the desired rate after a delay. The levodopa and decarboxylase enzyme inhibitor may be formulated in the expanding plug and released at the desired rate upon entry into the stomach.

Another embodiment of this invention may be achieved by formulating each of the drugs as pellets / beads, each with its own release profile and delay where applicable, and delivering the mixture of the three pellets in a shell using methods commonly known in the art. Furthermore, the proportions of the different types of pellets / beads may be altered or customized by a skilled artisan (*e.g.*, qualified physician or pharmacologist), based on an individual patient's conditions, such as weight, age, gender, ethnicity, and/or specific genetic backgrounds. Such customization may be effected with the aid of, or automatically executed by a computer program based on relevant parameters such as those described above.

Embodiments of the invention wherein each drug may be released at a different rate can be formulated as tri-layer (or multilayer if necessary) tablets. Each layer of the tablet may have a distinct release profile. For example, a tablet within a tablet with an immediate release coating wherein the innermost tablet would be formulated with the dopamine transport inhibitor, the outer portion of the tablet formulated with levodopa, and the outer coating formulated with decarboxylase enzyme inhibitor, in an appropriate ratio according to the teachings of the instant invention. In another preferred embodiment, the drugs may be formulated into tablets held in a recessed fashion within an annular ring of drug material, as described above. The recessed core may be formulated as a delayed release of dopamine transport inhibitor at the desired release profile; the annular ring may be formulated to give the desired release profile of levodopa (immediate release and sustained release delivery); and an outermost coating layer may give an immediate release of decarboxylase enzyme inhibitor.

Another embodiment uses the delivery system as described in U.S. patent application Ser. No. 10/191,298, wherein the dopamine transport inhibitor is formulated in the mantle and the expanding plug is a bilayer tablet. One layer of the bilayer tablet comprising levodopa formulated for sustained release delivery and the other layer comprising decarboxylase enzyme inhibitor formulated to release at the desired rate. Yet another embodiment of the invention could be achieved by formulating each of the drugs as pellets each with its own release profile and delay where applicable and delivering the mixture of the three pellets in a

shell as commonly understood by one of ordinary skill in the art.

In yet another example, the tablet is a longitudinally compressed tablet containing a plurality of precompressed inserts of the various compositions of the invention, mixtures thereof, excipients, and optionally a permeation enhancer. The precompressed inserts may each have different compositions (*e.g.*, the top insert may constitute the first IR portion, the next one or more inserts may constitute the substantially zero-order release rate second portion, *etc.* Drug is only released at the edge or surface of this tablet, which can result in zero-order kinetics in, for example, the second portion. In certain embodiments, the tablet may be encased in a sheath or shell, which has an insoluble, impermeable plug at one end to seal off the end, and has an opening (*e.g.,* orifice) at the opposite end to allow drug release from successive layers of inserts (see **Figure 1**). The thickness of each insert may be adjusted to accommodate different dosages. The overall shape of the device is not necessarily cylindrical, cubic column, *etc.*, but can be any desired shape or size.

In certain embodiments, the tablet is a trilayer tablet having an inner core that includes one or more drugs in an appropriate matrix of excipients (*e.g.*, HPMC, MCC, lactose) and is surrounded on two sides by a bioadhesive polymeric coating. Preferred bioadhesive polymeric coatings are a DOPA-BMA polymer and a mixture of poly(fumaric-co-sebacic) anhydride and EUDRAGIT™ RS PO. Other bioadhesive polymers are described in the section below.

In another example, the tablet is comprised of a multiplicity of bioadhesive-coated microspheres or beads that have been compressed into a tablet core and subsequently coated with a bioadhesive coating and one or more additional coatings (*e.g.*, enteric coatings). For example, in an illustrative embodiment as shown in **Figure 2**, different types of beads, each type with separate types and/or thickness of coatings, may be mixed together in desired or customized proportions to deliver varying amounts of first IR, second portion of zero-order release, and optionally second portion of IR, *etc.* The coatings on different types of beads may control the release timing of each type of beads.

Various drug-eluting devices are described in U.S. Patent Nos. 4,290,426, 5,256,440, 5,378,475, 5,773,019 and 6,797,283, the contents of which are incorporated herein by reference.

In one example, the drug-eluting device includes an inner reservoir comprising the effective agent; a first coating layer, which is essentially impermeable to the passage of the effective agent; and a second coating layer, which is permeable to the passage of the effective

agent. The first coating layer covers at least a portion of the inner reservoir; however, at least a small portion of the inner reservoir is not coated with the first coating layer (*e.g.*, there are one or more pores in the first coating layer). The second coating layer essentially completely covers the first coating layer and the uncoated portion of the inner reservoir. Typically, the first coating layer is a non-bioerodable or a slowly bioerodable polymer (*e.g.*, a polymer having a polymethylene backbone). For the present invention, one illustrative embodiment is shown in **Figure 3**, where the first coating is the bioadhesive coating, and the second coating is the first IR portion. The inner reservoir contains the second zero-order release portion, which may comprise one or a few layers to effect, for example, changing ratios of levodopa / carbidopa. One of these layers may also be the 3rd IR portion or the dopamine transporter inhibitor (see **Figure 4**).

In another example, the drug eluting device includes a multilayer core, often bilayer or more layers, formed of polymer matrices that swell upon contact with the fluids of the stomach or other GI fluids. At least one layer of the multilayer core includes a drug. A portion of the polymer matrices are surrounded by a band of insoluble material that prevents the covered portion of the polymer matrices from swelling and provides a segment of the dosage form that is of sufficient rigidity to withstand the contractions of the stomach. The core and the band of soluble material are coated with a bioadhesive polymeric coating. **Figure 5** provides an illustrative embodiment of this configuration. As shown, the three depicted layers represent the immediate-release composition layer **(IR)**, and two substantially zero-order release rate composition layers **(CR1** and **CR2)**. There may be more than two such substantially zero-order release rate composition layers, differing by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson disease therapeutic composition). A bioadhesive layer or patch (hatched lines) is shown to be on the outside wall of the shell encompassing the therapeutic compositions, which are successively released through an orifice close to the IR composition (proximal end).

In a further example, the drug eluting device is an osmotic delivery system. Typically, the reservoir of such devices contains osmotic agents to draw water across a semi-permeable membrane and a swelling polymer to push drug out of the device at a controlled rate. For example, **Figure 5** shows that the distal end of the shell may comprise a plug that can push the therapeutic compositions towards the orifice at the proximal end. The push mechanism can be any suitable means, such as a water-absorbing gel that swells when in contact with aqueous solution, or a rigid plate / plunger that can be driven by a micromotor (optionally

externally activated).

In yet another embodiment, there may be two or more reservoirs within a shell, each reservior coated by a bioadhesive layer as described above, and each reservior contains a different composition, such as different second doses designed to be released at successive times, or second zero-order release portion and the second IR portion (**Figure 6**).

In another embodiment (**Figure 7**), the composition may be formed as a cylinder or a column, or have a trapezoid profile (right panel). The compositions (*e.g.*, levodopa **72** and carbidopa **71**) are released starting from the top face and progressing in the order shown by the arrow. The top (beginning) of the dosage form has a different carbidopa / levodopa ratio from the bottom (end) of the dosage form.

In another embodiment (**Figure 8**), the first IR portion is formed as a layer, while one or more second portions (sustained zero-order release portion, *e.g.*, CR2) may be formulated as coated beads embedded in a layer of another sustained zero-order release sub-portion (*e.g.*, CR1). After the first IR portion is released, one sub-portion of the sustained zero-order release portion (*e.g.*, CR1) starts to release, while release of the other sub-portions (*e.g.*, CR2) is delayed due to the coating on the beads. There can be more than one layer and/or more than one types of beads according to this embodiment of the invention.

In another embodiment (**Figure 9**), the first IR portion **91** covers the bioadhesive layer **94**, which in turn covers the inner compositions, such as various sustained release (zero-order release) sub-portions (*e.g.*, **CR1 93**), and/or an optional ascending release portion (**92**), which may also be occupied by another sub-portion of sustained release (zero-order release). The first sub-portion of the zero-order release (**CR1 93**) may have a geometric shape (regular or irregular, symmetrical or asymmetrical) such that increasing or decreasing amounts of drugs may be released in unit time periods.

In another embodiment (**Figure 10**), drug release from the two sub-portions of zero-order release (**CR1 1002** and **CR2 1003**) is initiated from the inner core of a donut-shaped delivery device. After the outer IR layer **1001** is dissolved, holes on the bioadhesive layer **1004** encompassing the sub-portion(s) of zero-order release composition(s) may be release sequentially or simultaneously.

In another embodiment (**Figure 11**), the dosage form takes the shape of a rod, with the first IR portion **1101** situated at one or both ends (or on the surface (not shown)) of the rod. If there is one or more controlled release (zero-order release) sub-portion (such as **CR2 1103**), they are each sealed off by a substantially impermeable bioadhesive band **1104**, such that

their release is delayed, until the other controlled release sub-portions (such as **CR1 1102**) are substantially completely released (see **Figure 11**).

In certain variations of this embodiment, each of the substantially impermeable bioadhesive bands **1104** is an inert backing layer, which may or may not contain bioadhesive materials. The two **1104** layers separate the controlled release layer **1102** to a portion that is between the backing layers **1104** (the inside portion), and two portions that is outside the backing layers **1104** (the outside portions). The inside portion of **1102** is only exposed to solvents around the edge due to the presence of the two backing layers **1104**. In certain embodiments, one or both of the outside portions of **1102** may be absent, and/or one of the two immediate release portions **1101** is absent. One exemplary variant configuration is also shown in Figure 57.

Figure 12 shows yet another embodiment depicting a multilaminate bioadhesive buccal patch or tablet. The dosage form attaches to the mucosa surface (preferably through a bioadhesive layer attached to the **CR2** layer, optionally also the **CR1** layer, as described above), and sequentially releases the first IR **1202**, and one or more sub-portions (*e.g.*, **CR1 1203** and **CR2 1204**) of controlled release sub-portions of the zero-order release portion (second portion).

Figure 13 features a dose sipping system, where various types of beads corresponding to various sub-portions of controlled release (only two sub-portions, **CR1** and **CR2**, are shown as **1302**) are embedded in a matrix of the first IR portion **1301**, which in turn is deposited in a straw / tube. One end of the straw is sealed off by a porous plug **1303** to allow aqueous bodily fluid to seep in upon applying suction from the other end of the straw.

This embodiment also relates to a general concept for drug delivery, wherein a first portion of a multi-portion dosage form is formulated as a matrix for embedding one or more other portions of the same dosage form. In certain embodiments, the first portion is an immediate release (IR) formulation, and the other embedded portions are controlled release (CR) portions, each CR portion is optionally coated by a bioadhesive coat and/or a delayed release coat. Each CR portion may be formed as microparticles (*e.g.*, beads) suspended in the first portion (*e.g.*, IR portion) matrix. The disintegration of the matrix leads to the release of the embedded microparticles, which may re-adhere to the gut or other tissues (if coated by bioadhesive layer), and provided for sustained release.

This embodiment also relates to a general system for drug delivery, wherein therapeutic compositions are deposited at the end of a hollow tube sealed off by a porous

plug. The plug holds the therapeutic compositions inside the tube, but is also porous enough to allow liquid to come into the tube through the plug if a vaccum is generated inside the tube (such as by sipping or applying suction). The dissolved therapeutic compositions can then exit through the opposite end of the tube, *e.g.*, into the patient's mouth.

Figure 14 features a delivery device with a shell comprising a cap and a bioadhesive body. The cap is made of gelatin-type of material that is readily dissolved once the shell is internalized by a patient. The body of the shell comprises a bioadhesive material of the subject invention. Upon dissolution of the cap, the IR portion, and the substantially zero-order release portion (or sub-portions thereof) may be sequentially released as shown. Alternatively, the one or more CR sub-portions may be embedded within the IR matrix as described in other embodiments of the invention.

Figure 18 features yet another configuration of the delivery device, in which a **CR** portion **1801** is sandwiched between two adhesive layers **1802** (*e.g.*, a layered cross section) or inside one continuous adhesive layer **1802** (*e.g.*, configured as a filled tube). SPHEROMER™ I [p(FASA)] and SPHEROMER™ III are exemplary such bioadhesive layers (see, *e.g.*, Example 5 in WO 2007/002516). The portion / layer can (but need not) be substantially flat. In certain embodiments, there are two substantially flat adhesive layers **1802** sandwiching one **CR** layer **1801**. Components of the **CR** can be either released from surfaces not in contact with the adhesive parts **1802**, and/or through the adhesive materials if such materials are at least partially permeable. An immediate release portion **IR 1803** is coated over all or a part of the adhesive layer **1802**. In certain embodiments, the rapid dissolution of the **IR** portion exposes a **CR** surface not in contact with the adhesive material. In another embodiment, the dissolution of the **IR** portion does not substantially change the release rate of the **CR** portion. The tablet may be produced using methods such as those described in Examples 6-12 of WO 2007/002516.

Figure 19 features yet another configuration of the subject delivery device, which may be used in general to deliver any kind of drugs (or prodrugs, metablic precursors thereof, *etc.*). Although levodopa and/or carbidopa were used in the Examples to illustrate the delivery method, device and dosage form, it should be understood that the subject delivery devices (such as the one described in Figure 19), dosage form, and methods of making and using are not limited to these specific exemplary drug compositions described herein.

Thus according to this aspect of the invention, any drug to be delivered (*e.g.*, levodopa and/or carbidopa), optionally including a bioadhesive polymer composition, and/or

pharmaceutically acceptable excipients, may be formulated using the subject granulation-extrusion-spheronization process into multiparticulate pellets, which in turn may be dispersed in certain matrix materials, or simply encapsulated in capsules.

Specifically, appropriate amounts of the different ingredients are first weighed and mixed.

Suitable excipients for use in the subject granulation-extrusion-spheronization process include: Starcap-1500, starch-1500, and glycerine monostearate. In certain embodiments, the mixture is substantially free of microcrystalline cellulose.

In an exemplary embodiment, about 30-90%, about 40-85%, or about 50-80% (v/v) of the mixture (and the pellets formed therefrom) is effective ingredient (*e.g.*, drug composition), rather than excipients or polymers. Such loadings can be achieved using any drug or combination of drugs that are suitably cohesive, plastic, and engage in hydrogen bonding. Levodopa and carbidopa are examples of such drugs, though others will be known to or can be easily identified by those of skill in the art.

These different ingredients can then be blended together in any suitable device, such as a planetary type mixer (*e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for about 5-15 min.). Optionally, the blending process is done in small volume to reduce any possible loss of the ingredients due to their non-specific adherence to the blending device. The blending step is typically done to ensure the formation of a uniform dry mix of the ingredients, typically over a period of, *e.g.*, 5-15 min.

The dry mix is then granulated, *e.g.*, under low shear with a granulation fluid, so as to form a wet granulation. Granulation fluids may be purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of a polymeric composition in a chlorinated solvent or in a ketone, *etc.*

In certain embodiments, the granulation process is conducted in a small volume, such as in a 500-mL cylindrical vessel.

In certain embodiments, the granulation process is conducted with manual mixing, or conducted mechanically, *e.g.*, in a planetary type mixer (such as a Hobart Mixer with a 5-qt mixing bowl). If the Hobart Mixer is used, it can be operated at its speed setting #1, depending on the batch size. Other types of mechanical mixers may also be used, with their respective appropriate settings, to achieve substantially the same result.

Once the wet granulation is formed, it may be extruded through the screen of a screen-type extruder. In certain embodiments, a Caleva Model 20 (or Model 25) Extruder may be used, operating at 10-20 rpm, and forming breakable wet strands ("the extrudate"). The screen aperture may be set at 0.8, 1, or 1.5 mm. Other types of extruders may be used to achieve substantially the same result.

The extrudate may then be spheronized in a spheronizer. For example, a Caleva Model 250 spheronizer equipped with a 2.5-mm spheronization plate may be used, which may be operated at a speed of about 1000-2000 rpm, typically for 5-10 min., in order to form spheronized pellets. Other types of spheronizer may be used to achieve substantially the same result.

For certain effective ingredients, such as carbidopa, the extruding step and the spheronization step may be omitted.

The spheronized pellets may then be dried. The drying may be conducted in a fluidized bed drier, such as a Vector MFL.01 Micro Batch Fluid Bed System. If the Vector drier is used, it may be operated at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of about 50 °C. Alternatively, the pellets may be dried in an ACT (Applied Chemical Technology) fluidized bed drier, operating at an inlet air flow rate of 140-150 fpm (foot per minute) and an inlet air temperature of 104 °F. Other types of driers may also be used to achieve substantially the same result. Depending on the specific type of drugs / compositions, the drying temperature for a drier similar to the Vector drier may be between 35-70 °C, or 40-65 °C, or 45-60°C, or 45-55 °C, *etc.* The drying temperature for a drier similar to the ACT drier may be between 70-140 °F, or 80-130 °F, or 90-120°F, or 100-110 °F, *etc.*

In yet another embodiment, the spheronized pellets may be dried in an oven, such as a Precision gravity oven, operating at about 50 °C, for 4-48 hrs, or 8-24 hrs. Depending on the specific type of drugs / compositions, the oven drying temperature for a drier similar to the Precision gravity oven may be between 35-70 °C, or 40-65 °C, or 45-60°C, or 45-55 °C, *etc.*

The dried pellets may then be screened and/or classified. This can be done by using a stack of sieves, such as stainless steel sieves U.S. standard mesh sizes 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 45, or 60, *etc.*, and using a mechanical sieve shaker (*e.g.*, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min.). Particle size and distribution of pellet formulations can then be analyzed, and the classified pellets ranging from 0.25 mm (mesh # 60) to 2 mm (mesh # 10) may be selected for use or future formulation, such as additional film coating or other experimentation.

In certain embodiments, the formed pellets may be film-coated, *e.g.*, with a delayed-release coating (such as an entaric coating), a controlled-release (CR) coating, a bioadhesive polymeric composition, and/or a dispersion-promoting coating, *etc.*

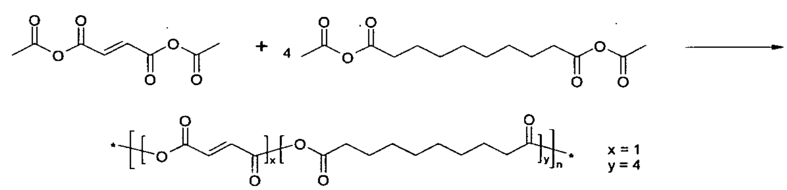
For example, the pellet core may be optionally surrounded by a CR coating, such as polymeric substance based on acrylates and/or methacrylates, *e.g.*, a EUDRAGIT™ polymer (sold by Rohm America, Inc.). Specific EUDRAGIT™ polymers can be selected having various permeability and water solubility, which properties can be pH dependent or pH independent. For example, EUDRAGIT™ RL, EUDRAGIT™ NE, and EUDRAGIT™ RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, which are present as salts and give rise to the permeability of the lacquer films. EUDRAGIT™ RL is freely permeable and EUDRAGIT™ RS is slightly permeable, independent of pH. In contrast, the permeability of EUDRAGIT™ L is pH dependent. EUDRAGIT™ L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water, but becomes increasingly soluble in a neutral to weakly alkaline solution by forming salts with alkalis. Above pH 5.0, the polymer becomes increasingly permeable. If desired, two or more types of polymeric substances may be mixed for use as the CR coating. Other polymers suitable for CR coatings, such as ethyl cellulose and cellulose acetate, can also be used in the CR coating. In certain embodiments, the CR coating may comprise one or more suitable polymers, such as a combination of two or more of the polymers discussed above.

Optionally, the pellets may also be coated by a bioadhesive polymeric composition. The adhesive material may facilitate the adhesion of the pellets to a desired surface, such as a preferred GI tract surface. For example, the pellets / beads may be coated by a top-layer of a bioadhesive polymer such as SPHEROMER™ I [p(FASA)], SPHEROMER™ II, SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof (see, *e.g.*, Example 14 of WO 2007/002516).

The SPHEROMER™ III or IV bioadhesive polymers, citric acid, and hydroxypropyl cellulose components are common to both the tablet formulation and the multiparticulate extended release capsule formulations. Additional excipients used in the multilayer extended release tablet formulations include magnesium stearate, succinic acid, hypromellose, corn starch, Ludipress®, butylated hydroxytoluene and p[FA:SA] or (SPHEROMER™ I). Poly[fumaric-co-sebacic acid anhydride] or p[FA:SA] (SPHEROMER™ I), is a bioadhesive polymer developed by Applicants that is similar to SPHEROMER™ III. All other excipients

utilized in the multilayer extended release tablet formulations meet USP/NF specifications.

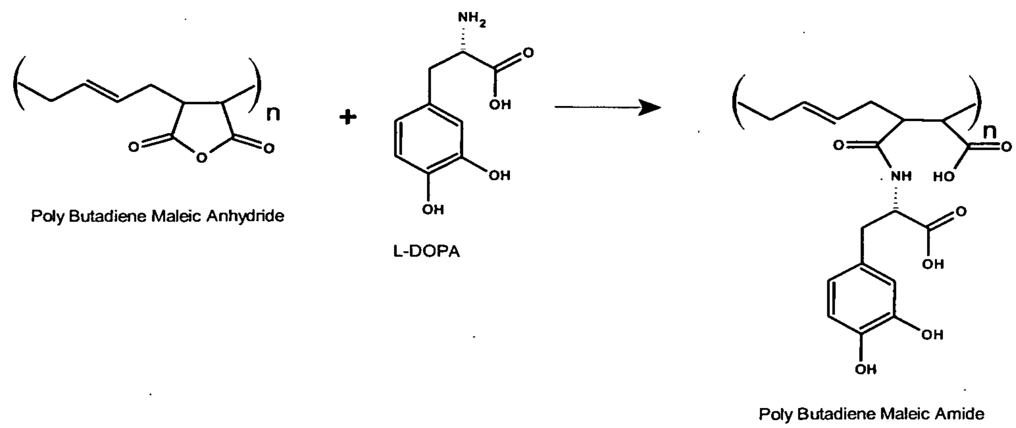
The SPHEROMER™ I polymer is a polyanhydride copolymer of fumaric anhydride and sebacic anhydride reacted through polycondensation. Applicants have demonstrated the synergystic effect of SPHEROMER™ I, in *in-vitro* and animal studies, when combining the polymer with SPHEROMER™ III and using them as bioadhesives in improving the GI residence time and bioavailability of drugs in solid oral dosage forms. The chemical structures of fumaric anhydride and sebacic anhydride and their reaction to form SPHEROMER™ I are depicted below:



Applicants have determined that, even with the inclusion of only a small percentage of SPHEROMER™ I, SPHEROMER™ III exhibits much better stability under a wide range of pHs.

The SPHEROMER™ III polymer was developed by Applicants. Applicants have demonstrated the utility and safety of polyanhydride polymers as bioadhesives for improving the GI residence time and bioavailability of drugs in solid oral dosage forms in both animal and human studies. Recent research has focused on the usefulness of bioadhesives fashioned after the adhesives secreted by marine mussels (*Mytilus edulis*). Levodopa, a naturally-occurring, phenolic, amino acid widely for treatment of Parkinson's disease, has been identified as a key bioadhesive component of mussel adhesive. Synthetic polymers that are hydrophobic hydrogen bond with GI mucus, and have solubility parameters similar to mucus glycoproteins that exhibit bioadhesion. Examples of such polymers include degradable and non-degradable polyanhydrides.

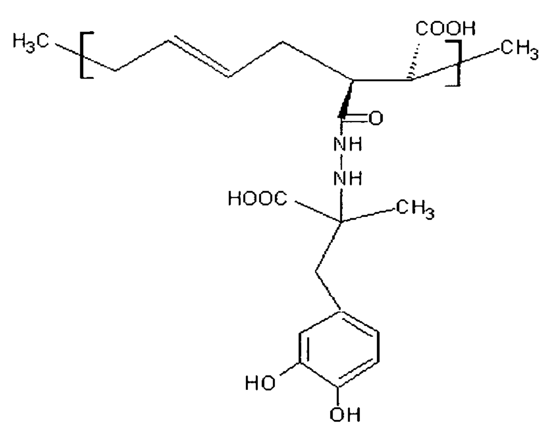
Logically, a polymer combining hydrophobic polyanhydrides and bioadhesive, phenolic amino acids such as levodopa should demonstrate superior bioadhesive properties. A non-degradable polyanhydride, poly(butadiene-maleic anhydride) or BMA, was used as the backbone polymer, and levodopa was chemically grafted onto the polymer to form a polyamide copolymer (L-DOPA-BMA, SPHEROMER™ III). The chemical structures and their reaction are depicted below:



Ex vitro tensile testing of this polymer has indicated superior bioadhesive properties that correlate with improved gastric residence time of bioadhesive tablets formulated with SPHEROMER™ III in beagle dogs.

Levodopa was covalently grafted to the BMA backbone and *in vitro* degradation studies have shown that less than 2% of the bound levodopa was released during 3 days of incubation in various biological fluids (liver and brain homogenates) and buffers. Toxicokinetic studies in beagle dogs have demonstrated that exogenous levodopa derived from degradation of SPHEROMER™ III polymer in bioadhesive tablets is not detectable in plasma.

In addition, the combination of the non-degradable poly(butadiene-maleic anhydride) or BMA as the backbone polymer and carbidopa, chemically grafted onto the backbone polymer, resulted in a polyamide copolymer (CARBIDOPA-BMA, SPHEROMER™ IV polymer). The SPHEROMER™ IV polymer is a butadiene maleic anhydride copolymer grafted with carbidopa, and its monomer is represented by the following structure (without the terminal $-CH_3$ groups in polymer repeats):



PCT/US2006/024352 (filed on June 23, 2006, titled "Bioadhesive Polymers") provides more detailed description of the SPHEROMER™ I, II, III, and IV polymers. The entire contents of the PCT application PCT/US2006/024352 is incorporated herein by reference.

In certain embodiments, the functions of a CR coating and bioadhesive coating can be combined in a single layer by using a mixture of polymers including a bioadhesive polymeric material and a polymer suitable for controlled release, *i.e.*, a single layer may be both the CR layer and the bioadhesive layer of a particle.

Optionally, the pellets can also be film-coated with an additional layer of a so-called "non-functional polymer," such as OPADRY™ II, EUDRAGIT™ E, ACRYL-EZE™, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol, polyvinylacetate, polyanhydride, *etc.* (see, *e.g.*, Example 14 of WO 2007/002516). This layer may serve as a dispersion-promoting coating that inhibits clumping and aggregation of the particles during dispersion. In embodiments wherein the pellets are further compressed with excipients to form tablets, this layer is preferably sufficiently strong or resilient to remain substantially intact during the compression process. This layer may also be protected by including a cushioning material among the excipients of the tablet matrix such as spray dried lactose, various grades of microcrystalline cellulose, glyceryl monostearate, pregelatinized starch, compressible sugar, PEG 8000, dicalcium phosphate (Di-Tab), calciumhydrogenphosphate (Bekapress D2) and cellactose.

The coating material (such as bioadhesive polymeric materials and/or functional / nonfunctonal polymers) may be dissolved in an appropriate solvent, such as methylene chloride (*e.g.*, for SPHEROMER™ I), methanol (*e.g.*, for SPHEROMER™ III), a binary mixture of methanol and methylene chloride (*e.g.*, for SPHEROMER™ I and SPHEROMER™ III), methanol or a binary mixture of ethanol and water (3:1 v/v) (*e.g.*, for SPHEROMER™ IV), or methanol, ethanol, or isopropanol, or their binary mixture with acetone (*e.g.*, functional or non-functional polymer).

The film coating may be performed in a fluidized bed coater, such as a Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liters per minute), and an inlet air temperature of about 25-45 °C, or about 30-40 °C, depending on the specific drugs and coatings (*e.g.*, 25-30 °C for SPHEROMER™ I-coated levodopa-carbidopa; about 35 °C for SPHEROMER™ III-coated levodopa-carbidopa, *etc.*). If the Vector System is used, the pellets may be pre-warmed at 35

°C for 2-5 min., and after film-coating, post-dried at about 30 °C for about 15-30 min.

Alternatively, pellets may be coated in a fluid bed processor, such as a Fluid Air Model 5 fluid bed processor equipped with a Wurster insert, operating at an inlet air flow rate of about 70 cfm (cubic foot per minute) and an inlet air temperature of about 35 °C. For this type of fluid bed processor, the pellets may be pre-warmed at 40 °C for 5-7 min., and after film-coating, post-dried at about 35 °C for about 30 min.

Other types of coaters may also be used to achieve substantially the same result.

Different lots or even different types of the same pellets produced using the subject method may optionally be mixed, *e.g.*, by using a blender (such as a GlobePharma Maxiblend Blender equipped with an 8-qt stainless steel V-shell).

In certain embodiments, different types of pellets may be mixed. For example, some pellets may have no coating and are simply a core comprising the effective ingredients. Other pellets, even if identically in core structure, may further be coated by one or more types of coatings, *e.g.*, bioadhesive coating, delayed-release coating, controlled-release coating, and/or dispersion-promoting coating, *etc.*

In certain embodiments, pellets produced using the methods of the invention may be encapsulated in capsules, such as hard gelatin capsules or pullulan capsules (NPcaps™), each with a predetermined amount of effective ingredients. For example, if the effective ingredients are carbidopa and levodopa, 50 mg carbidopa and 200 mg of the levodopa may be encapsulated.

In certain embodiments, pellets produced using the methods of the invention may be dispersed in a matrix material to assist the delivery of the effective ingredients of the pellets. There are at least two preferred configurations according to this embodiment of the invention.

Figure 19 shows a schematic drawing (not to scale) of one such configuration. In Figure 19, the active components **1901** (such as the pellets produced using the subject method, which are not necessarily round in shape) are embedded / dispersed within an inactive material or carrier matrix **1902**. The carrier matrix **1902** can rapidly disintegrate, *e.g.*, dissolve substantially completely (superdisintegrant) within about 15 minutes, 10 minutes, 8 minutes, 7 minutes, 6 minutes, 5 minutes, 3 minutes, 2 minutes, or about 1 minute or less. See, *e.g.*, Example 15 of WO 2007/002516.

The inactive material **1902** may additionally comprise one or more cushioning materials dispersed throughout, *e.g.*, sufficient to protect the active components **1901** when preparing the delivery device, by substantially absorbing the impact of compacting, and/or

reducing friction on the surface of the particles **1901** (to prevent damaging the substructure of the particles, see below).

In certain embodiments, in order to incorporate these particles into a tablet matrix, a filler/binder must be used in the tableting process that will not allow the destruction of the pellets during the tableting process. Materials that are suitable for this purpose include, but are not limited to, microcrystalline cellulose (AVICEL®), soy polysaccharide (EMCOSOY®), pre-gelatinized starches (STARCH® 1500, NATIONAL® 1551), and polyethylene glycols (CARBOWAX®). These materials may be present in the range of about 5%-75% (w/w), and preferably between about 25%-50% (w/w).

In addition, disintegrants are added to the tablets in order to disperse the beads once the tablet is ingested. Suitable disintegrants include, but are not limited to: crosslinked sodium carboxymethyl cellulose (AC-DI-SOL®), sodium starch glycolate (EXPLOTAB®, PRIMOJEL®), and crosslinked polyvinylpolypyrrolidone (Plasone-XL). These materials may be present in the range of about 3%-15% (w/w), with a preferred range of about 5%-10% (w/w).

Lubricants are also added to assure proper tableting, and these can include, but are not limited to: magnesium stearate, calcium stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, and hydrogenated vegetable oil. These lubricants should be present in amounts from about 0.1%-10% (w/w), with a preferred range of about 0.3%-3.0% (w/w).

The particles **1901** may be in any suitable size and shape (rods, beads, or other regular or irregular shapes). In certain embodiments, the particles are beads with a diameter of less than about 2 mm, about 1.5 mm, about 1 mm, about 0.8 mm, about 0.7 mm, about 0.5 mm, about 0.3 mm, or about 0.1 mm. In certain embodiments, the pellets are substantially homogeneous in size and/or shape. In certain embodiments, for pellets with levodopa and/or carbidopa as effective ingredient, the pellet size is about 0.8 – 1 mm. Particles are formulated to these sizes in order to enable high drug loading when needed.

As described above, particles **1901** may have substructures, such as various coating layers surrounding a drug / prodrug core. Although the following describes the substructures using a bead with levodopa and/or carbidopa as effective ingredient, it is an illustrative example only, and the description also applies to other shapes of particles with other effective ingredients.

The core by itself may be an immediate release portion, or may have release-controlling components (*e.g.*, CR portion), and preferably, the core is made by extrusion, such

as the granulation-extrusion-spheronization process described in, *e.g.*, Example 13 of WO 2007/002516. The core is optionally surrounded by a CR coating, such as polymeric substance based on acrylates and/or methacrylates, *e.g.*, a EUDRAGIT™ polymer (sold by Rohm America, Inc.). Specific EUDRAGIT™ polymers can be selected having various permeability and water solubility, which properties can be pH dependent or pH independent. For example, EUDRAGIT™ RL, EUDRAGIT™ NE, and EUDRAGIT™ RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, which are present as salts and give rise to the permeability of the lacquer films. EUDRAGIT™ RL is freely permeable and EUDRAGIT™ RS is slightly permeable, independent of pH. In contrast, the permeability of EUDRAGIT™ L is pH dependent. EUDRAGIT™ L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water, but becomes increasingly soluble in a neutral to weakly alkaline solution by forming salts with alkalis. Above pH 5.0, the polymer becomes increasingly permeable. If desired, two or more types of polymeric substances may be mixed for use as the CR coating. Other polymers suitable for CR coatings, such as ethyl cellulose and cellulose acetate, can be used in the CR coating. The CR coating may comprise one or more suitable polymers, such as a combination of two or more of the polymers discussed above.

Optionally, the CR coating is itself coated by a layer of adhesive material that facilitates the adhesion of the particles / beads to a desired surface, such as a preferred GI tract surface. Various suitable adhesive materials are described herein above. For example, the pellets / beads may be coated by a top-layer of a bioadhesive polymer such as SPHEROMER™ I [p(FASA)], SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof (see, *e.g.*, Example 14 of WO 2007/002516). In certain embodiments, the functions of a CR coating and bioadhesive coating can be combined in a single layer by using a mixture of polymers including a bioadhesive polymeric material and a polymer suitable for controlled release, *i.e.*, a single layer may be both the CR layer and the bioadhesive layer of a particle.

Optionally, pellets can be further film-coated with an additional layer of a so-called “non-functional polymer” such as OPADRY™ II, EUDRAGIT™ E, ACRYL-EZE™, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol, polyvinylacetate, polyanhydride, *etc.* (see, *e.g.*, Example 14 of WO 2007/002516). This layer may serve as a dispersion-promoting coating that inhibits clumping and aggregation of the particles during dispersion. In embodiments wherein the pellets are further compressed with excipients to

form tablets, this layer is preferably sufficiently strong or resilient to remain substantially intact during the compression process. This layer may also be protected by including a cushioning material among the excipients of the tablet matrix such as spray dried lactose, various grades of microcrystalline cellulose, glyceryl monostearate, pregelatinized starch, compressible sugar, PEG 8000, dicalcium phosphate (Di-Tab), calciumhydrogenphosphate (Bekapress D2) and cellactose, *e.g.*, so that the the outer layer is not significantly scratched or gouged during the compression process, and/or retains its dispersion-promoting properties.

Optionally, an **IR** portion is included in the particle, such as over the dispersion-promoting coating, or between the dispersion-promoting coating and the adhesive layer, *etc.*

In an alternative embodiment, particles **1901** are not embedded within the inactive material **1902**, but are instead disposed loose in a capsule that dissolves and releases the particles in the GI tract.

It should be understood that any other embodiments of the invention, such as those utilizing beads / pellets (see *e.g.*, Figures 2, 8, 13, *etc.*), may additionally or alternatively use the coated pellets shown in Figure 19.

Figure 20 features yet another embodiment of the delivery device, in which particles described herein above (*e.g.*, with respect to Figure 19) are embedded within a slow eroding material **2001** (*e.g.*, that gradually erodes over 30 minutes, 45 minutes, 1 hr, 2 hrs, 4 hrs, 6 hrs, or longer). At least a portion of the eroding material **2001** is covered by an **IR** portion **2002**, which disintegrates relatively rapidly to expose a surface of eroding material **2001**. A portion of the slow eroding material **2001** is also optionally covered by a passive polymer support layer and/or an adhesive material **2003** as described herein above. In certain embodiments, the IR portion **2002** may be disposed on the adhesive layer **2003** instead of the eroding material 2001 as depicted. See, *e.g.*, Example 16 of WO 2007/002516.

According to a related aspect of the invention, any drug to be delivered (*e.g.*, levodopa and/or carbidopa), optionally including a bioadhesive polymer composition, and/or pharmaceutically acceptable excipients, may also be formulated as a multilayer tablet.

Specifically, different ingredients (such as those described above) are weighed and mixed. These ingredients, possibly with the exception of any lubricants, can then be blended together in any suitable device, such as an end-over-end ATR rotator (*e.g.*, model RKVS), or a planetary type mixer (*e.g.*, Hobart Mixer). Optionally, the blending process is done in small volume to reduce any possible loss of the ingredients due to their non-specific adherence to the blending device. The blending step is typically done to ensure the formation of a uniform

dry mix of the ingredients, typically over a period of, *e.g.*, 5-15 min.

The dry mix is then granulated, *e.g.*, under low shear with a granulation fluid, so as to form a wet granulation. Granulation fluids may be purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of a polymeric composition in a chlorinated solvent or in a ketone, *etc.*

In certain embodiments, the granulation process is conducted in a small volume, such as in a 500-mL cylindrical vessel.

In certain embodiments, the granulation process is conducted with manual mixing, or conducted mechanically, *e.g.*, in a planetary type mixer (such as a Hobart Mixer with a 5-qt mixing bowl). If the Hobart Mixer is used, it can be operated at its speed setting #1, depending on the batch size. Other types of mechanical mixers may also be used, with their respective appropriate settings, to achieve substantially the same result.

Once the wet granulation is formed, it is dried. In certain embodiments, the wet granulation is dried in an oven (*e.g.*, a Precision gravity oven, operating at about 50 °C, for 8-24 hrs; or similar appropriate conditions for other types of ovens). Alternatively, the granulation may be dried in a fluidized bed drier, such as a Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of about 50 °C. The drying temperature is generally around 50 °C. However, depending on different types of drugs / compositions, the temperature may be 35-70 °C, or 40-65 °C, or 45-60°C, or 45-55 °C, *etc.*

The dried granulation is then ground, *e.g.*, by using a pestle in a mortar, optionally followed by sieving the ground material, *e.g.*, through an approrpiate-sized screen (such as a U.S. Std. mesh # 60 screen), depending on the desired size of the granules.

At this point, the sieved granulation may be blended with a lubricant. In certain embodiments, the blending is conducted using an end-over-end ATR rotator (*e.g.*, model RKVS). In certain embodiments, the blending is conducted using a planetary type mixer (*e.g.*, Hobart Mixer, operating at the speed setting #1, for 5-15 min.). As a result, a uniformly lubricated dry mix is formed, which is then ready for compression.

Optionally, before compression, the lubricated dry mix may be passed through a sieve or screen, *e.g.*, a U.S. Std. mesh # 60 screen.

Different components of the pharmaceutical composition (*e.g.*, the effective

ingredients, any bioadhesive polymeric materials, or other coatings, *etc.*) may be prepared as a mixture or separately using the subject methods. Once the dry mixes are formed, they can be compressed into single layer or multilayer tablets. For example, the lubricated dry mix may be pressed into tablets, such as by using a single-station manual tablet press (*e.g.*, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set). If the GlobePharma machine is used, tablets may be prepared, *e.g.*, at a pressure ranging from 250 to 4000 pounds per square inch (psi), and a compression time of, *e.g.*, 1 to 4 seconds. Other machines may also be used to achieve substantially the same result.

Alternatively, in certain embodiments, tablets may be produced with wet granulation of active ingredients followed by direct compression (see, *e.g.*, Example 6 of WO 2007/002516).

In certain embodiments, multilayer tablets may be produced, with each layer comprising a different ingredient. In these embodiments, a single-station manual tablet press (*e.g.*, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set) may be used in several steps to produce the multilayer tablets. For example, for a bilayer tablet, the compression process may include:

(1) adding the first layer blend into the die cavity, optionally followed by manually tapping it, *e.g.*, using a stainless steel spatula;

(2) adding the second layer blend into the die cavity;

(3) pre-compressing the two layers together, *e.g.*, at a pressure ranging from 250 to 500 pounds per square inch (psi) and a compression time of, *e.g.*, 1 to 5 seconds.

(4) compressing the pre-compacted layers together, *e.g.*, at a pressure ranging from 1000 to 4000 pounds per square inch (psi) and a compression time of, *e.g.*, 1 to 4 seconds.

The process can be repeated or modified if more than two layers of ingredients are to be used.

In certain embodiments, the tablet can be made with a pre-compressed insert with effective ingredients. Such pre-compressed inserts may be produced with direct compression (see, *e.g.*, Example 10 of WO 2007/002516). The same press machine may be used for this process. For example, if using the GlobePharma Manual Tablet Compaction Machine MTCM-I machine, tablet inserts may be prepared, *e.g.*, at a pressure ranging from 500 to 1000 pounds per square inch (psi), and a compression time of, *e.g.*, 1 to 2 seconds. Other machines may also be used to achieve substantially the same result. The pre-compressed

insert may be used as one of the layers (*e.g.*, the second layer) in the tablet, or embedded in the middle of another layer (*e.g.*, the second layer). See, for example, Example 10 of WO 2007/002516.

Optionally, the tablets may be coated with one or more coating compositions, such as in the form of successive layers. The coating compositions may include bioadhesive layers, delayed release layers, controlled-release layers, and/or other functional / non-functional polymers *etc.* (*supra*). For example, tablets may be film-coated for this purpose, using a pan coater (*e.g.*, O'Hara Labcoat, operating at an inlet air flow rate of about 60 cfm (cubic foot per minute) and an inlet air temperature of about 35 °C). The tablets may be pre-warmed at 35 °C for 5-10 min., and after film coating, may be post-dried at about 30 °C for about 15-30 min. Other coaters may also be used to achieve substantially the same result.

Figure 21 features yet another embodiment of the delivery device, in which particles **2100** described herein above (*e.g.*, with respect to Figure 19) are dispersed on the surface of a bioadhesive film **2101**. The film may optionally be dried or cured, *e.g.*, without disrupting the particle adhesion. The film may then be placed in a capsule **2102** for administration to a patient. If needed, the film may first be folded or cut to a suitable shape or size. Once administered to a patient, the capsule releases the film, which then rehydrates (if necessary) and adheres to a mucosal surface, allowing the particles spreaded and adhered thereto to release the active components.

In certain embodiments, the subject composition is formulated for variable dosing, such as customized dosing for individual patients.

In addition, more than one type of drugs can be present in a tablet or a drug eluting device of the invention, *e.g.*, for combination therapy with other pharmaceutical compositions effective for treating PD or other movement disorders (see below). The drugs can be evenly distributed throughout a medicament or can be heterogeneously distributed in a medicament, such that one drug is fully or partially released before a second drug. See different embodiments of the drug devices and/or layering in other parts of this specification.

Dosage forms of the invention typically weigh at least about 50 mg. Dosage forms (such as the various shell designs of the invention) can also weigh at least 100 mg, at least 150 mg, at least 250 mg, at least 500 mg, or at least 1000 mg, *etc.*

Dosage forms (*e.g*, capsule or tablet) of the invention typically measure at least 2 mm in one direction. For example, dosage forms can measure at least 5 mm, at least 10 mm, at least 15 mm or at least 20 mm in one direction. Typically, the diameter of the dosage forms is

2 to 40 mm, preferably 10 to 30 mm such as 20 to 26 mm. Mini-tablets have a diameter of 2 mm to about 5 mm. Such dosage forms can measure at least 2 mm, at least 5 mm, at least 10 mm, at least 15 mm or least 20 mm in a second direction and, optionally, a third direction. Preferably, the dosage form is of a size that facilitates swallowing by a subject.

The volume of a typical dosage form of the invention is at least 0.008 mL, at least 0.01 mL, at least 0.05 mL, at least 0.1 mL, at least 0.125 mL, at least 0.2 mL, at least 0.3 mL, at least 0.4 mL or at least 0.5 mL.

Dosage forms of the invention may be a tablet that can be of any suitable size and shape, for example, round, oval polygonal or pillow-shaped, and optionally bears nonfunctional surface markings. Especially in the case of coated tablets, they are preferably designed to be swallowed whole and are therefore typically not provided with a breaking score. Tablets of the invention can be packaged in a container, *e.g.*, accompanied by a package insert providing pertinent information such as, for example, dosage and administration information, contraindications, precautions, drug interactions and adverse reactions.

To produce a dosage form that can release at least two or three drugs at two or three different rates, and with preprogrammed delays, special dosage forms are used. For example, in the embodiments of the invention wherein different dosage forms of levodopa / carbidopa are designed to be released concomitantly, the drugs may be formulated as bilayer (or other multilayer) tablets or shells (*e.g.*, stacked layer of cakes, each may represent an independent formulation). Alternatively, the drugs may be formulated as a tablet within a tablet or bead (not limited to two nested layers). Optionally, a bioadhesive layer may be coated over part or all of a gel capsule (or other forms of delivery device) to enhance the stay of the device within a certain area of the GI tract, such as the intestine.

The various embodiments described herein are only a sample of numerous possible configurations to deliver the subject dosage forms. Other variations may be readily envisioned based on the principals and teachings of the instant specification. For example, various other drug-eluting devices are described in U.S. Patent Nos. 4,290,426, 5,256,440, 5,378,475, 5,773,019 and 6,797,283, the contents of which are incorporated herein by reference.

In these and other embodiments of the invention, the various bioadhesive coatings that can be used are described in detail in the section below.

Many of the different embodiments described above may be implemented by using

rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a subject pharmaceutical composition at a particular target site. The biodegradable polymers undergo chemical decomposition to form soluble monomers or soluble polymer units. The biodegradation of polymers usually involves chemically or enzymatically catalyzed hydrolysis. Representative biodegradable polymers comprise a member selected from biodegradable poly(amides), poly(amino acids), poly(esters), poly(lactic acid), poly(glycolic acid), poly(orthoesters), poly(anhydrides), biodegradable poly(dehydropyrans), and poly(dioxinones). The polymers are known to the art in Controlled Release of Drugs, by Rosoff, Ch. 2, pp. 53-95 (1989); and in U.S. Pat. Nos. 3,811,444; 3,962,414; 4,066,747; 4,070,347; 4,079,038; and 4,093,709.

In certain embodiments, representative dosage forms include hydrogel matrix containing a plurality of tiny pills or other particles. The hydrogel matrix comprises a hydrophilic polymer, such as selected from a polysaccharide, agar, agarose, natural gum, alkali alginate including sodium alginate, carrageenan, fucoidan, furcellaran, laminaran, hypnea, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust bean gum, pectin, amylopectin, gelatin and a hydrophilic colloid. The hydrogel matrix comprises a plurality of tiny pills or particles (such as 4 to 50), each tiny pill or particle may comprise a different portion of the subject compositions (*e.g.*, IR, *etc.*). Representative of wall-forming materials include a triglyceryl ester selected from glyceryl tristearate, glyceryl monostearate, glyceryl dipalmitate, glyceryl laureate, glyceryl didecenoate and glyceryl tridecenoate. Other wall forming materials comprise polyvinyl acetate phthalate, methylcellulose phthalate, and microporous vinyl olefins. Procedures for manufacturing tiny pills are disclosed in U.S. Pat. Nos. 4,434,153; 4,721,613; 4,853,229; 2,996,431; 3,139,383 and 4,752,470, which are incorporated by reference herein.

In still other embodiments, the invention employs a dosage form comprising a polymer that releases a drug by diffusion, flux through pores, or by rupture of a polymer matrix. The dosage form matrix can be made by procedures known to the polymer art. An example of providing a dosage form comprises blending a pharmaceutically acceptable carrier, like polyethylene glycol, with a known dose of the subject pharmaceutical composition, and adding it to a silastic medical grade elastomer with a cross-linking agent,

like stannous octanoate, followed by casting in a mold. The step is repeated for each successive layer. The system is allowed to set, *e.g.*, for 1 hour, to provide the dosage form. Representative polymers suitable for manufacturing the dosage form include olefin and vinyl polymers, condensation polymers, carbohydrate polymers, and silicon polymers as represented by poly(ethylene), poly(propylene), poly(vinyl acetate), poly(methyl acrylate), poly(isobutyl methacrylate), poly(alginate), poly(amide), and poly(silicone). The polymers and manufacturing procedures are known in Polymers, by Coleman *et al.*, Vol. **31**, pp. 1187-1230 (1990); *Drug Carrier Systems*, by Roerdink *et al.*, Vol. 9, pp. 57-109 (1989); *Adv. Drug Delivery Rev.*, by Leong *et al.*, Vol. 1, pp. 199-233 (1987); *Handbook of Common Polymers*, Compiled by Roff *et al.*, (1971) published by CRC Press; and U.S. Pat. No. 3,992,518.

Other exemplary embodiments of the delivery devices are described in the subsection below, and in the Example section of the application.

Other Exemplary Delivery Devices and Systems

This subsection describes additional exemplary delivery systems that can be used to deliver any of a large spectrum of compounds (*e.g.*, drugs, prodrugs, metabolic precursors, *etc.*), especially those with limited absorption windows in upper GI (*e.g.*, stomach).

An exemplary list of compounds that can be delivered using the subject dosage forms and/or delivery devices includes, but not limited to: metformin, acyclovir, ranitidine, riboflavin, chlorthiazide, gabapentin, losartin potassium, ganciclovir, cimetidine, minocycline, fexofenadine, bupropion, orlistat, captopril, diphenhydramine, tripelennamine, chlorpheniramine maleate, promethazine, omeprazole, prostaglandin, carbenoxolane, sucralphate, isosorbide, quinidine, enalapril, nifedipine, verapamil, diltiazem, nadolol, timolol, pindolol, salbutamol, terbutaline, carbuterol, broxaterol, aminophylline, cyclizine, cinnarizine, domperidone, alizapride, vincristine, megestrol acetate, daunorubicin, actinomycin, adriamycin, etoposide, 5-fluorouracil, indomethacin, sulindac, piroxicam, ibuprofen, naproxen, ketoprofen, temazepam, lorazepam, flunitrazepam, amantadine, ampicillin, amoxicillin, erythromycin, tetracyclines, cyanocobalamin, amino acids, iron or calcium salts of essential trace elements, or pharmacologically acceptable salts of the above.

In certain embodiments of the invention, illustrated in **Figure 22**, the oral solid dosage form is a monolayer matrix tablet **100**, containing one or more drug(s), pharmaceutically acceptable excipients or salts thereof, optionally one or more permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in a single monolithic layer **110**. Various drug release profiles can be achieved by tailoring the composition and/or

configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR) or controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from all sides. The cross-section of this dosage form is illustrated in **Figure 22.**

In certain embodiments of the invention, illustrated in **Figure 23,** the oral solid dosage form is a bilayer tablet **200**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in two monolithic layers **210** and **220**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In these embodiments, the tablet is designed to provide immediate release (IR) or controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from layer **210**, and optionally an extended release (ER) of one or more soluble drugs from the other layer **220**. One or more bioadhesive polymer compositions are incorporated into layer **220**. This layer may optionally contain release rate controlling polymer(s), pore former(s), and/or other polymer(s) to regulate its rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 23.**

In certain embodiments of the invention, illustrated in **Figure 24,** the oral solid dosage form is a trilayer tablet **300**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in three monolithic layers **310, 320** and **330**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In these embodiments, the tablet is designed to provide controlled release (CR) of one or more soluble, poorly soluble or insoluble drug from layer **310**, and optionally an extended release (ER) of one or more soluble drugs from the other layers **320** and **330**. One or more bioadhesive polymer compositions may be incorporated into layers **320** and **330**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 24.**

In certain embodiments of the invention, illustrated in **Figure 25,** the oral solid dosage form is a trilayer tablet with a pre-compressed insert **400**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in three layers **410, 420** and **430**, and a pre-compressed tablet **440**, inserted in layer **410**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each

layer and the pre-compressed insert. In this embodiment, the tablet is designed to provide ascending controlled release (aCR) of one or more poorly soluble or insoluble drugs from layer **410** and pre-compressed insert **440,** and optionally an extended release (ER) of one or more soluble drugs from layers **420** and **430**. One or more bioadhesive polymer compositions may be incorporated into layers **420** and **430**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 25.**

In certain embodiments of the invention, illustrated in **Figure 26,** the oral solid dosage form is a trilayer tablet **500**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, one or more bioadhesive polymer compositions, formulated in three monolithic layers **510, 520** and **530.** Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In these embodiments, the tablet layers are designed to provide immediate release (IR) layer **520**, and/or controlled release (CR) layer **510**, of one or more soluble, poorly soluble or insoluble drugs, and optionally an extended release (ER) layer **530**, of one or more soluble drugs. One or more bioadhesive polymer compositions are incorporated into layer **530**. This layer may option-ally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 26.**

In certain embodiments of the invention, illustrated in **Figure 27,** the oral solid dosage form is a trilayer tablet with a pre-compressed insert **600**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in three layers **610, 620** and **630**, and a pre-compressed tablet **640**, inserted in layer **610**, laying approximately on the middle of the bottom layer **630**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the pre-compressed insert. In this embodiment, the tablet layers and the pre-compressed insert are designed to provide immediate release (IR) from layer **620**, and ascending controlled release (aCR) from layer **610** and pre-compressed insert **640**, of one or more soluble, poorly soluble or insoluble drug, and optionally an extended release (ER), from layer **630,** of one or more soluble drugs. One or more bioadhesive polymer compositions is incorporated into layer **630.** This layer may contain release rate controlling polymer(s), pore former(s), and other

polymer(s) to regulate its rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 27**.

In certain embodiments of the invention, illustrated in **Figure 28,** the oral solid dosage form is a multilayer extended release tablet **700**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in four monolithic layers **710, 720, 730** and **740**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet layers are designed to provide immediate release (IR), from layer **720**, and controlled release (CR), from layer **710**, of one or more soluble, poorly soluble or insoluble drugs, and optionally an extended release (ER), from layers **730** and/or **740**, of one or more soluble drugs. One or more bioadhesive polymer compositions is incorporated into layers **730** and **740**. These layers may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 28**.

In certain embodiments of the invention, illustrated in **Figure 29,** the oral solid dosage form is a multilayer extended release tablet with a pre-compressed insert **800**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in four monolithic layers, **810, 820, 830** and **840,** and a pre-compressed tablet **850**, inserted in the center of layer **810**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the pre-compressed insert. In this embodiment, the tablet layers are designed to provide immediate release (IR), from layer **820**, and ascending controlled release (aCR), from layer **810** and pre-comrpessed insert **850**, of one or more soluble, poorly soluble or insoluble drug, and optionally an extended release (ER), layers **830** and/or **840**, of one or more soluble drug. One or more bioadhesive polymer compositions is incorporated into layers **830** and **840**. These layers may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 29**.

In certain embodiments of the invention, illustrated in **Figure 30,** the oral solid dosage form is a monolayer matrix tablet, **900**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single monolithic

layer **910**. The tablet may be optionally coated with a release rate-controlling membrane **920**, before applying the bioadhesive coating membrane **930**. Optionally the release rate-controlling and bioadhesive membranes, **920** and **930**, may have plasticizer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of the core tablet and the coating membrane(s). In this embodiment, the tablet is designed to provide controlled release (CR) of one or more soluble, poorly soluble or insoluble drug from all sides. The cross-section of this dosage form is illustrated in **Figure 30**.

In certain embodiments of the invention, illustrated in **Figure 31,** the oral solid dosage form is a monolayer tablet with a pre-compressed insert **1000**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single layer **1010**, and a pre-compressed tablet **1020**, inserted in the center of that layer. The tablet may be optionally coated with a release rate-controlling membrane **1030**, before applying the bioadhesive coating membrane **1040**. Optionally the release rate-controlling and bioadhesive membranes **1030** and **1040**, may have plasticizer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of the core tablet and the coating membrane(s). In this embodiment, the tablet is designed to provide controlled release (CR) or ascending controlled release (aCR) of one or more soluble, poorly soluble or insoluble drug from all sides. The cross-section of this dosage form is illustrated in **Figure 31**.

In certain embodiments of the invention, illustrated in **Figure 32,** the oral solid dosage form is a trilayer tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **1100**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in three layers, **1110, 1120** and **1130**, and granulated, spheronized, pelletized, or mini-tableted multiparticulates **1140**, dispersed in layer **1110**. The multiparticulates are fillm-coated with one or more bioadhesive polymer compositions **1150**. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive pellets. The top-coat membrane may serve different purposes, including functioning as a moisture and/or

oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying layer **1110**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide controlled release (CR) of one or more soluble, poorly soluble or insoluble drug from bioadhesive multiparticulates **1140/1150** and possibly layer **1110**, and optionally an extended release (ER) of one or more soluble drug from layers **1120** and/or **1130**. One or more bioadhesive polymer compositions is incorporated into layers **1120** and **1130**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 32**.

In certain embodiments of the invention, illustrated in **Figure 33,** the oral solid dosage form is a trilayer tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **1200**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in three layers, **1210, 1220** and **1230**, and granulated, spheronized, pelletized, or mini-tableted multiparticulates **1240**, dispersed in layer **1210**. The multiparticulates are film-coated with one or more bioadhesive polymer compositions **1250**. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive pellets. The top-coat membrane may serve different purposes, including functioning as a moisture and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying layer **1210**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR), from layer **1220**, and controlled release (CR), from bioadhesive multiparticulates **1240/1250** and possibly layer **1210**, of one or more soluble, poorly soluble or insoluble drug, and optionally an extended release (ER) of one or more soluble drug from layers **1240** and/or **1250**. One or more bioadhesive polymer compositions is incorporated into layers **1240** and **1250**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 33**.

In certain embodiments of the invention, illustrated in **Figure 34,** the oral solid dosage

form is a multilayer extended release tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **1300**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in four layers, **1310**, **1320**, **1330**, and **1340**, and granulated, spheronized, pelletized, or mini-tableted multiparticulates **1350**, dispersed in layer **1310**. The multiparticulates are film-coated with one or more bioadhesive polymer compositions **1360**. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive multiparticulates. The top-coat membrane may serve different purposes, including functioning as a moisture and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying layer **1310**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the multiparticulates. In this embodiment, the tablet is designed to provide immediate release (IR), from layer **1320**, and controlled release (CR), from bioadhesive multiparticulates **1350/1360** and possibly layer **1310**, of one or more soluble, poorly soluble or insoluble drug, and optionally an extended release (ER) of one or more soluble drug from layers **1330** and/or **1340**. One or more bioadhesive polymer compositions is incorporated into layers **1330** and **1340**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 34**.

In certain embodiments of the invention, illustrated in **Figure 35,** the solid oral dosage form is a longitudinally compressed tablet **1400**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single monolithic layer **1410**. The tablet is sealed peripherally with a layer of bioadhesive composition **1420**, leaving the upper and lower sides, **1430A** and **1430B**, of the tablet available for drug release. Optionally, the tablet may be coated with a release rate-controlling layer before applying the bioadhesive coating. Optionally, the release rate-controlling and bioadhesive coatings may have plasticizer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. Various drug release profiles, and preferably and more advantageously, zero-order release profiles, can be achieved by tailoring

the composition of the core matrix. The cross-section of this dosage form is illustrated in **Figure 35.**

In certain embodiments of the invention, illustrated in **Figure 36,** the solid oral dosage form is a longitudinally compressed tablet **1500**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in two monolithic layers, **1510** and **1520**. The tablet is sealed peripherally with a layer of bioadhesive composition **1530**, leaving the upper and lower sides, **1540A** and **1540B**, of the tablet available for drug release. Optionally, the bioadhesive coating may have plasticizer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR) of one or more soluble, poorly soluble or insoluble drugs from layer **1510**, and controlled release (CR) of one or more soluble drugs from the other layer **1520**. The cross-section of this dosage form is illustrated in **Figure 36.**

In certain embodiments of the invention, illustrated in **Figure 37,** the solid oral dosage form is a longitudinally compressed tablet **1600**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in four monolithic layers, **1610**, **1620**, **1630** and **1640**. The tablet is sealed peripherally with a layer of bioadhesive composition **1650**, leaving the upper and lower sides, **1660A** and **1660B**, of the tablet available for drug release. Optionally, the bioadhesive coating may have plasticizer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR) of one or more soluble, poorly soluble or insoluble drugs from layer **1610**, and controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from layer **1640**, followed by fast release of one or more soluble, poorly soluble or insoluble drugs from layer **1640**. Layers **1610** and **1630** are separated by a slow dissolving passive matrix **1620**, which may completely dissolve following the depletion of drug(s) from layer **1640**. The cross-section of this dosage form is illustrated in **Figure 37**.

In certain embodiments of the invention, illustrated in **Figure 38,** the solid oral dosage form is a longitudinally compressed tablet **1700**, containing one or more drugs,

pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in four monolithic layers, **1710**, **1720**, **1730** and **1740**. The tablet is sealed peripherally with a layer of bioadhesive composition **1750**, leaving the upper and lower sides, **1760A** and **1760B**, of the tablet available for drug release. Optionally, the bioadhesive coating may have plasticizer(s), pore former(s), and other polymer(s) to regulate its rigidity and permeability. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer. In this embodiment, the tablet is designed to provide immediate release (IR) or fast controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from layer **1710**, followed by delayed release of one or more soluble, poorly soluble or insoluble drugs from layer **1730** in an immediate release (IR) or fast controlled release (CR) fashion. Layer **1740** is a slow dissolving passive matrix **1720**, which completely dissolves following the depletion of drug(s) from layer **1710**. Layers **1710** and **1730** are separated by a slow dissolving passive matrix **1720**, which may completely dissolve following the depletion of drug(s) from layers **1710** and **1730**. The cross-section of this dosage form is illustrated in **Figure 38**.

In certain embodiments of the invention, illustrated in **Figure 39**, the oral solid dosage form **1800**, is a hard shell two-piece capsule **1810**, containing a monolayer matrix tablet **1820**, and a trilayer tablet **1830**. The monolayer tablet **1820**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single layer matrix. The trilayer tablet **1830**, contains one or more drug, pharmaceutically acceptable excipients, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in three monolithic layers, **1840, 1850** and **1860**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each tablet. In this embodiment, the tablets are designed to provide immediate release (IR) of one or more soluble, poorly soluble or insoluble drugs from monolayer tablet **1820**, and controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs from trilayer tablet **1830**. One or more bioadhesive polymer compositions is incorporated into layers **1850** and **1860**. These layers may have identical or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 39**.

In certain embodiments of the invention, illustrated in **Figure 40,** the oral solid dosage form **1900**, is a hard shell two-piece capsule **1910**, containing a multiplicity of monolayer matrix tablets, **1920**, **1930**, **1940**, **1950**, and **1960**. The monolayer tablets, contains one or more drug, pharmaceutically acceptable excipients, optionally permeation and/or dissolution enhancers, and optionally one or more bioadhesive polymer compositions, formulated in a single layer matrix. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each tablet. In this embodiment, the tablets are designed to provide immediate release (IR) and controlled release (CR) of one or more soluble, poorly soluble or insoluble drugs. The cross-section of this dosage form is illustrated in **Figure 40**.

In certain embodiments of the invention, illustrated in **Figure 41,** the oral solid dosage form is a multilayer extended release tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **2000**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions, formulated in four layers, **2010**, **2020**, **2030**, and **2040**, and granulated, spheronized, pelletized, or mini-tableted multiparticulates, **2050, 2060 and 2070**, respectively dispersed in layers **2020**, **2030**, and **2040**. The multiparticulates may be optionally film-coated with one or more bioadhesive polymer compositions. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive pellets. The top-coat membrane may serve different purposes, including functioning as a moisture and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying layers. Various drug release profiles can be achieved by tailoring the composition and/or configuration of each layer and the multiparticulates. In this embodiment, the tablet is designed to provide immediate release (IR), from layer **2010**, and controlled release (CR), from multiparticulates **2050** and possibly layer **2020,** of one or more soluble, poorly soluble or insoluble drug. Optionally one or more soluble, poorly soluble or insoluble drug is released from the multiparticulates **2060** and **2070**, and their respective layers, **2030** and **2040**, in an extended release (ER) fashion. One or more bioadhesive polymer compositions is incorporated into layers **2060** and **2070**. These layers may have same or different compositions, and may optionally contain release rate controlling polymer(s), pore former(s), and other polymer(s) to regulate their rigidity and permeability. The cross-section of this dosage form is illustrated in **Figure 41**.

In certain embodiments of the invention, illustrated in **Figure 42,** the oral solid dosage form is a monolayer tablet with granulated, spheronized, pelletized, or mini-tableted multiparticulates **2100**, containing one or more drugs, pharmaceutically acceptable excipients or salts thereof, optionally permeation and/or dissolution enhancers, and one or more bioadhesive polymer compositions. The tablet is formulated as a single rapidly disintegrating matrix **2110**, and contains a solid dispersion of granulated, spheronized, pelletized, or mini-tableted multiparticulates **2120**. The multiparticulates are film-coated with one or more bioadhesive polymer compositions **2130**. A release rate-controlling membrane may be optionally applied onto the multiparticulates as a sub-coat before applying the bioadhesive layer. A rapidly dissolving non-functional membrane may be applied as a top-coat onto the bioadhesive multiparticulates. The top-coat membrane may serve different purposes, including functioning as a moisture and/or oxygen barrier, and isolating the bioadhesive multiparticulates from each other immediately upon the release from the carrying matrix **2110**. Various drug release profiles can be achieved by tailoring the composition and/or configuration of the matrix and the multiparticulates. In this embodiment, the tablet is designed to provide immediate release (IR), from matrix **2110**, and controlled release (CR), from bioadhesive multiparticulates **2120/2130**, of one or more soluble, poorly soluble or insoluble drug. The cross-section of this dosage form is illustrated in **Figure 42**.

In certain embodiments of the invention, illustrated in Figure 57 (not necessarily to scale) as one design of the subject Levodopa-Carbidopa extended release (XL) tablets, the extended / controlled release layer is sandwiched between two backing layers, which backing layers may or may not contain bioadhesive materials (see Examples 27 and 28). On top of one (or both) of the backing layers is an immediate release layer that quickly disintegrates and dissolves. Drug release from the extended / controlled release layer, however, is much slower. Due to the presence of the inactive backing layers, drug release from the extended / controlled release layer begins around the exposed edge or side of the sandwiched-in extended / controlled release layer, and gradually goes towards the inner portion of the extended / controlled release layer.

Optionally, the thickness and density of the extended / controlled release layer can be designed such, that at certain point, erosion of the extended / controlled release layer will result in the breaking of the tablet into two halves (not necessarily equal halves), thus creating larger erosion surfaces. The increased drug release rate towards the end of the drug release period can produce a delayed or ascending release profile, which may be desirable in certain

embodiments (see above).

These various embodiments are only a sample of numerous possible configurations to deliver the subject dosage forms. Other variations may be readily envisioned based on the principals and teachings of the instant specification.

In these and other embodiments of the invention, the various bioadhesive coatings that can be used are described in detail in the section below. The terms "bioadhesive polymer composition" and "bioadhesive polymer material" is intended to encompass both compositions where the polymer itself is bioadhesive, as well as compositions where a non- or poorly bioadhesive polymer is combined with a compound that imparts bioadhesive properties to the composition as a whole, as described in detail herein.

Preferably, other than the desired immediate release doses, drug eluting devices of the invention release the drug or prodrug contained therein with zero-order kinetics.

Many of the different embodiments described above may be implemented by using rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a subject pharmaceutical composition at a particular target site.

In certain embodiments, representative dosage forms include hydrogel matrix containing a plurality of tiny pills or other particles (see **Figure 2**). The hydrogel matrix comprises a hydrophilic polymer, such as selected from a polysaccharide, agar, agarose, natural gum, alkali alginate including sodium alginate, carrageenan, fucoidan, furcellaran, laminaran, hypnea, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust bean gum, pectin, amylopectin, gelatin and a hydrophilic colloid. The hydrogel matrix comprises a plurality of tiny pills or particles (such as 4 to 50), each tiny pill or particle may comprise a different ratio of decarboxylase inhibitor / levodopa, either as first or second IR or the second zero-order release portion, *etc.* The tiny pills or particles may comprise a release rate controlling wall of 0.01 mm to 10 mm thickness to provide for the timed release of drug in different portions. Representative of wall-forming materials include a triglyceryl ester selected from glyceryl tristearate, glyceryl monostearate, glyceryl dipalmitate, glyceryl laureate, glyceryl didecenoate and glyceryl tridecenoate. Other wall forming materials comprise polyvinyl acetate phthalate, methylcellulose phthalate, and microporous vinyl olefins. Procedures for manufacturing tiny pills are disclosed in U.S. Pat. Nos. 4,434,153;

4,721,613; 4,853,229; 2,996,431; 3,139,383 and 4,752,470, which are incorporated by reference herein.

In certain embodiments, the drug-releasing beads are characterized by a dissolution profile wherein 0 to 20% of the beads undergo dissolution and release the drug in 0 to 2 hours, 20 to 40% undergo dissolution and release the drug in 2 to 4 hours, 40 to 60% exhibit dissolution and release in 4 to 6 hours, 60 to 80% in 6 to 8 hours, and 80 to 100% in 8 to 10 hours or longer. The drug-releasing beads can include a central composition or core comprising a drug and pharmaceutically acceptable composition forming ingredients including a lubricant, antioxidant, and buffer. The beads comprise increasing doses of drug, for example, 0.1 mg, 0.2 mg, 0.5 mg, and so forth to a high dose. The beads are coated with a release rate-controlling polymer that can be selected utilizing the dissolution profile disclosed above. The manufacture of the beads can be adapted from, for example, Liu *et al.*, *Inter. J. of Pharm.* **112**: 105-116, 1994; Liu *et al.*, *Inter. J. of Pharm.* **112**: 117-124, 1994; *Pharm. Sci.*, by Remington, 14th Ed. pp. 1626-1628 (1970); Fincher *et al.*, *J. Pharm. Sci.* **57**: 1825-1835, 1968; and U.S. Pat. No. 4,083,949.

Another dosage form provided by the invention comprises a multiplicity of layers (see **Figures 1, 3, 4**, *etc.*). The phrase "multiplicity of layers" typically denotes 2 to 6 layers in contacting lamination (can be more layers if necessary). The multiplicity of layers are positioned consecutively, that is, one layer after another in order, with a first exposed layer, the sixth layer in contact with the fifth layer and its exposed surface coated with a drug impermeable polymer. The sixth layer is coated with a drug impermeable polymer to insure release of the subject pharmaceutical composition from the first layer to the sixth layer. The biodegradable polymers undergo chemical decomposition to form soluble monomers or soluble polymer units. The biodegradation of polymers usually involves chemically or enzymatically catalyzed hydrolysis. Representative of biodegradable polymers acceptable for an increase drug loading in each layer of from 5 to 50 wt % over the first and successive layers wherein the first layer comprises 100 ng. Representative biodegradable polymers comprise a member selected from biodegradable poly(amides), poly(amino acids), poly(esters), poly(lactic acid), poly(glycolic acid), poly(orthoesters), poly(anhydrides), biodegradable poly(dehydropyrans), and poly(dioxinones). The polymers are known to the art in Controlled Release of Drugs, by Rosoff, Ch. 2, pp. 53-95 (1989); and in U.S. Pat. Nos. 3,811,444; 3,962,414; 4,066,747; 4,070,347; 4,079,038; and 4,093,709.

In still other embodiments, the invention employs a dosage form comprising a

polymer that releases a drug by diffusion, flux through pores, or by rupture of a polymer matrix. The drug delivery polymeric system delivers a substantially zero-order release portion of the pharmaceutical composition may optionally comprise an inhibitor / levodopa ratio gradient, wherein the gradient is, for example, a descent in inhibitor / levodopa ratio from a beginning or initial ratio to a final, or lower ratio (comparably less inhibitor). The dosage form comprises an exposed surface at the beginning dose and a distant nonexposed surface at the final dose. The nonexposed surface is coated with a pharmaceutically acceptable material impermeable to the passage of drug. The dosage form structure provides for a delivery of drug at a relatively sustained level, with an optionally changing (*e.g.*, decreasing) inhibitor / levodopa ratio from the beginning to the final delivered dose of the second portion of the dosage form. The ratio may also be different in the first and second (if present) IR (or other substantially ascending dose portion) according to the instant invention.

The dosage form matrix can be made by procedures known to the polymer art. In one manufacture, 3 to 5 or more casting compositions are independently prepared wherein each casting composition comprises a portion of the dosage form, with each portion overlayered from, for example, a high to low inhibitor / levodopa ratio in the zero-order release dosage portion (second portion). This provides a series of layers that come together to provide a unit polymer matrix with an optionally varying inhibitor / levodopa ratio gradient. In another manufacture, the lower ratio portion is cast first followed by laminating with layers of ascending ratio portions to provide a polymer matrix with an inhibitor / levodopa ratio gradient. An example of providing a dosage form comprises blending a pharmaceutically acceptable carrier, like polyethylene glycol, with a known dose of the subject pharmaceutical composition, and adding it to a silastic medical grade elastomer with a cross-linking agent, like stannous octanoate, followed by casting in a mold. The step is repeated for each successive layer. The system is allowed to set, *e.g.*, for 1 hour, to provide the dosage form. Representative polymers suitable for manufacturing the dosage form include olefin and vinyl polymers, condensation polymers, carbohydrate polymers, and silicon polymers as represented by poly(ethylene), poly(propylene), poly(vinyl acetate), poly(methyl acrylate), poly(isobutyl methacrylate), poly(alginate), poly(amide), and poly(silicone). The polymers and manufacturing procedures are known in Polymers, by Coleman *et al.*, Vol. **31**, pp. 1187-1230 (1990); *Drug Carrier Systems*, by Roerdink *et al.*, Vol. 9, pp. 57-109 (1989); *Adv. Drug Delivery Rev.*, by Leong *et al.*, Vol. 1, pp. 199-233 (1987); *Handbook of Common Polymers*, Compiled by Roff *et al.*, (1971) published by CRC Press; and U.S. Pat. No. 3,992,518.

In yet other embodiments, the subject pharmaceutical compositions are delivered by way of a transdermal patch, a buccal patch, or a buccal tablet. A patch is generally a flat hollow device with a permeable membrane on one side and also some form of adhesive to maintain the patch in place on the patient's skin, with the membrane in contact with the skin so that the medication can diffuse out of the patch reservoir and into and through the skin. The outer side of the patch is formed of an impermeable layer of material, and the membrane side and the outer side are joined around the perimeter of the patch, forming a reservoir for the medication and carrier between the two layers.

Patch technology is based on the ability to hold an active ingredient in constant contact with the epidermis. Over substantial periods of time, drug molecules, held in such a state, will eventually find their way into the bloodstream. Thus, patch technology relies on the ability of the human body to pick up drug molecules through the skin. Transdermal drug delivery using patch technology has recently been applied for delivery of nicotine, in an effort to assist smokers in quitting, the delivery of nitroglycerine to angina sufferers, the delivery of replacement hormones in post-menopausal women, *etc.* These conventional drug delivery systems comprise a patch with an active ingredient such as a drug incorporated therein, the patch also including an adhesive for attachment to the skin so as to place the active ingredient in close proximity to the skin. Exemplary patch technologies are available from Ciba-Geigy Corporation and Alza Corporation. Such transdermal delivery devices can be readily adapted for use with the subject pharmaceutical compositions.

The flux of the subject pharmaceutical compositions across the skin can be modulated by changing either (a) the resistance (the diffusion coefficient), or (b) the driving force (the solubility of the drug in the stratum corneum and consequently the gradient for diffusion). Various methods can be used to increase skin permeation by the subject reuptake inhibitors, including penetration enhancers, use of pro-drug versions, superfluous vehicles, iontophoresis, phonophoresis, macroflux with micro projections, and thermophoresis. Many enhancer compositions have been developed to change one or both of these factors. See, for example, U.S. Pat. Nos. 4,006,218; 3,551,154; and 3,472,931, for example, respectively describe the use of dimethylsulfoxide (DMSO), dimethyl formamide (DMF), and N,N-dimethylacetamide (DMA) for enhancing the absorption of topically applied drugs through the stratum corneum. Combinations of enhancers comprising diethylene glycol monoethyl or monomethyl ether with propylene glycol monolaurate and methyl laurate are disclosed in U.S. Pat. No. 4,973,468. A dual enhancer comprising glycerol monolaurate and ethanol for

the transdermal delivery of drugs is shown in U.S. Pat. No. 4,820,720. U.S. Pat. No. 5,006,342 lists numerous enhancers for transdermal drug administration comprising fatty acid esters or fatty alcohol ethers of C2 to C4 alkanediols, where each fatty acid/alcohol portion of the ester/ether is of about 8 to 22 carbon atoms. U.S. Pat. No. 4,863,970 shows penetration-enhancing compositions for topical application comprising an active permeant contained in a penetration-enhancing vehicle containing specified amounts of one or more cell-envelope disordering compounds such as oleic acid, oleyl alcohol, and glycerol esters of oleic acid; a C2 or C3 alkanol; and an inert diluent such as water. Other examples are included in the teachings of U.S. Pat. No. 4,933,184 which discloses the use of menthol as a penetration enhancer; U.S. Pat. No. 5,229,130 discloses the use of vegetable oil (soybean and/or coconut oil) as a penetration enhancer; and U.S. Pat. No. 4,440,777 discloses the use of eucalyptol as a penetration enhancer.

The patch preferably comprises a drug-impermeable backing layer. Suitable examples of drug-impermeable backing layers which may be used for transdermal or medicated patches include films or sheets of polyolefins, polyesters, polyurethanes, polyvinyl alcohols, polyvinyl chlorides, polyvinylidene chloride, polyamides, ethylene-vinyl acetate copolymer (EVA), ethylene-ethylacrylate copolymer (EEA), vinyl acetate-vinyl chloride copolymer, cellulose acetate, ethyl cellulose, metal vapor deposited films or sheets thereof, rubber sheets or films, expanded synthetic resin sheets or films, non-woven fabrics, fabrics, knitted fabrics, paper and foils. Preferred drug-impermeable, elastic backing materials are selected from polyethylene terephthalate (PET), polyurethane, ethylene-vinyl acetate copolymer (EVA), plasticized polyvinylchloride, woven and non-woven fabric. Especially preferred is non-woven polyethyleneterephthalate (PET). Other backings will be readily apparent to those skilled artisan.

The dosage formulations described above, in the forms of cores of tablets and drug eluting devices of the invention, contain one or more excipients, carriers or diluents. These excipients, carriers or diluents can be selected, for example, to control the disintegration rate of a tablet or drug eluting device to fit the desired release profile according to the instant invention. In addition, the one or more carriers (additives) and/or diluents may be pharmaceutically acceptable.

The phrase “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the

subject regulators from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

Typical excipients to be added to a capsule formulation include, but are not limited to: fillers such as microcrystalline cellulose, soy polysaccharides, calcium phosphate dihydrate, calcium sulfate, lactose, sucrose, sorbitol, or any other inert filler. In addition, there can be flow aids such as fumed silicon dioxide, silica gel, magnesium stearate, calcium stearate or any other materials that impart good flow properties. A lubricant can also be added if desired, such as polyethylene glycol, leucine, glyceryl behenate, magnesium stearate or calcium stearate.

In certain embodiments, the disintegration time of a particular composition (such as the immediate release composition) may be less than the gastric (or small/large intestinal) retention time. In certain embodiments, the disintegration time of a tablet is at least 25% of the gastric retention time, at least 50% of the gastric retention time or at least 75% of the gastric retention time. In other embodiments, the disintegration time of a composition may be formulated to effect a substantially zero-order release, over a period of 2, 4, 6, 8, 12, or 24 hours, for instance.

The formulations can conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy. All methods include bringing into association the drug with the carrier or diluent which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the agent with the carriers and then, if necessary, dividing the

product into unit dosages thereof. It will be understood by those skilled in the art that any vehicle or carrier conventionally employed and which is inert with respect to the active agent, and preferably does not interfere with bioadhesiveness, may be utilized for preparing and administering the pharmaceutical compositions of the present invention. Illustrative of such vehicles and carriers are those described, for example, in *Remington's Pharmaceutical Sciences*, 18th ed. (1990), the disclosure of which is incorporated herein by reference.

Examples of carriers and diluents include pharmaceutically accepted hydrogels such as alginate, chitosan, methylmethacrylates, cellulose and derivatives thereof (microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose, ethylcellulose), agarose and Povidone^{TM}, kaolin, magnesium stearate, starch, lactose, sucrose, density-controlling agents such as barium sulfate and oils, dissolution enhancers such as aspartic acid, citric acid, glutamic acid, tartartic acid, sodium bicarbonate, sodium carbonate, sodium phosphate, glycine, tricine, Tromethamine, and TRIS.

The excipients, carriers or diluents can also be selected to control the time until a dosage form detaches from a mucosal membrane. In particular, the addition of one or more disintegrating agents will reduce the time until a tablet or drug eluting device detaches. Alternatively or in combination with the disintegrating agents, an agent that interferes with the mucosa-tablet / device adhesion can be used to control the time until detachment occurs.

As set out above, certain embodiments of the present pharmaceutical compositions may contain a basic functional group, such as amino or alkylamino, and are thus capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. The term "pharmaceutically acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include but are not limited to following: 2-hydroxyethanesulfonate, 2-naphthalenesulfonate, 3-hydroxy-2-naphthoate, 3-phenylpropionate, acetate, adipate, alginate, amsonate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bisulfate, bitartrate, borate, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate, carbonate, citrate, clavulariate, cyclopentanepropionate, digluconate, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, fumarate, gluceptate, glucoheptanoate, gluconate, glutamate, glycerophosphate, glycollylarsanilate, hemisulfate, heptanoate, hexafluorophosphate,

hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, laurylsulphonate, malate, maleate, mandelate, mesylate, methanesulfonate, methylbromide, methylnitrate, methylsulfate, mucate, naphthylate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, palmitate, pamoate, pantothenate, pectinate, persulfate, phosphate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosaliculate, suramate, tannate, tartrate, teoclate, thiocyanate, tosylate, triethiodide, undecanoate, and valerate salts, and the like. (See, for example, Berge *et al.*, "Pharmaceutical Salts", *J. Pharm. Sci.* **66**: 1-19, 1977).

In certain embodiments, the pharmaceutically acceptable salts of the subject compounds include the conventional non-toxic salts of the compounds, *e.g.*, from non-toxic organic or inorganic acids. Particularly suitable are salts of weak acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, hydriodic, cinnamic, gluconic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, maleic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, and magnesium salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, tromethamin, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge *et al.*, *supra*).

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and

magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Pharmaceutically acceptable antioxidants may also be included. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

VII. *Controlled Release / Bioadhesive Layer*

In certain embodiments of the invention, the subject dosage form is administered orally to the gastrointestinal (GI) tract. In such embodiments, it is desirable that the drug not be delivered substantially beyond the desired site of action and eliminated before it has had a chance to exert a topical effect or to pass into the bloodstream, particularly in the context of avoiding the gastric emptying and its adverse contribution to the On-Off effect. Thus, it is desirable that the subject drug delivery system adhere to the lining of the appropriate viscus, such that its contents can be delivered as a function of proximity and duration of contact.

An orally ingested product can adhere to either the epithelial surface or the mucus lining of the GI tract. For the delivery of bioactive substances, it can be advantageous to have a polymeric drug delivery device adhere to the epithelium or to the mucous layer. Bioadhesion in the GI tract may proceed in two stages: (1) viscoelastic deformation at the point of contact of the synthetic material into the mucus substrate, and (2) formation of bonds between the adhesive synthetic material and the mucus or the epithelial cells. In general, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds, and/or (iii) secondary chemical bonds (*e.g.*, ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bioadhesive properties, include dispersive interactions (*e.g.*, van der Waals interactions) and stronger specific interactions, which include hydrogen bonds. The hydrophilic functional groups primarily responsible for forming hydrogen bonds are the hydroxyl and the carboxylic groups.

In certain embodiments, the subject dosage forms having increased gastrointestinal retention time. For purposes of this invention, gastric residence time is the time required for a dosage form to transit through the stomach to the pyloric sphincter. For example, a dosage form of the invention has a gastric residence time of at least 3 hours, at least 4 hours, at least 6 hours, at least 8 hours or at least 12 hours. The dosage forms of the invention may also have an increased retention time in the small and/or large intestine, or in the area of the gastrointestinal tract that absorbs the drug contained in the dosage form. For example, dosage forms of the invention can be retained in the small intestine (or one or two portions thereof, selected from the duodenum, the jejunum and the ileum) for at least 6 hours, at least 8 hours or at least 12 hours, such as from 16 to 18 hours. For dosage forms having an enteric coating or an equivalent, the increased gastric residence time may not be applicable. These dosage forms, as a whole, include a bioadhesive polymeric coating that is applied to at least one surface of the tablet or drug eluting device.

Certain polymers for use in the subject invention are described in more details below.

Polymers

I. Bioadhesives

a. Polymers

Suitable bioadhesive polymeric coatings are disclosed in U.S. Patent Nos. 6,197,346, 6,217,908 and 6,365,187 (the contents of which are incorporated herein by reference), and include soluble and insoluble, biodegradable and nonbiodegradable polymers. These can be hydrogels or thermoplastics, homopolymers, copolymers or blends, and/or natural or synthetic polymers. The preferred polymers are synthetic polymers, with controlled synthesis and degradation characteristics. Particularly preferred polymers are anhydride copolymers of fumaric acid and sebacic acid (P(FA:SA)), which have exceptionally good bioadhesive properties when administered to the GI tract. Examples of P(FA:SA) copolymers include those having a 1:99 to 99:1 ratio of fumaric acid to sebacic acid, such as 5:95 to 75:25, for example, 10:90 to 60:40 or at least 15:85 to 25:75. Specific examples of such copolymers have a 20:80 or a 50:50 ratio of fumaric acid to sebacic acid.

Polymers used in dosage forms of the invention produce a bioadhesive interaction (fracture strength) of at least 100 N/m^2 (10 mN/cm^2) when applied to the mucosal surface of rat intestine. The fracture strength of the dosage forms is advantageously at least 250 N/m^2, at least 500 N/m^2 or at least 1000 N/m^2. For example, the fracture strength of a polymer-containing dosage form can be from 100 to 500 N/m^2. The forces described herein refer to

measurements made upon rat intestinal mucosa, unless otherwise stated. The same adhesive measurements made on a different species of animal will differ from those obtained using rats. This difference is attributed to both compositional and geometrical variations in the mucous layers of different animal species as well as cellular variations in the mucosal epithelium. However, the data shows that the same general trends prevail no matter what animal is studied (*i.e.*, P(FA:SA) produces stronger adhesions than polylactic acid (PLA) in rats, sheep, pigs, *etc.*). For example, the fracture strength of dosage forms of the invention on rat intestine is generally at least 125 N/m^2, such as at least 150 N/m^2, at least 250 N/m^2, at least 500 N/m^2 or at least 1000 N/m^2.

The fracture strength of a dosage form can be measured according to the methods disclosed by Duchene *et al.* Briefly, the dosage form is attached on one side to a tensile tester and is contacted with a testing surface (*e.g.*, a mucosal membrane) on the opposite surface. The tensile tester measures the force required to displace the dosage form from the testing surface. Common tensile testers include a Texture Analyzer and the Instron tensile tester.

In the preferred method for mucoadhesive testing, dosage forms are pressed using flat-faced tooling, 0.3750" (9.525 mm) in diameter. Dosage form weight will depend on composition; in most cases, the dosage forms have a final weight of 200 mg. These dosage forms are then glued to a plastic 10 mm diameter probe using a common, fast-drying cyanoacrylate adhesive. Once the dosage forms are firmly adhered to the probe, the probe is attached to the Texture Analyzer. The Texture Analyzer is fitted with a 1 kg load cell for maximum sensitivity. The following settings are used:

Pre-Test Speed	0.4 mm / sec	Stop Plot At	Final Position
Test Speed	0.1 mm / sec	Tare Mode	Auto
Post-Test Speed	0.1 mm / sec	Delay Acquisition	Off
Applied Force	20.0 g	Advanced Options	On
Return Distance	0 mm	Proportional Gain	0
Contact Time	420 s	Integral Gain	0
Trigger Type	Auto	Differential Gain	0
Trigger Force	0.5 g	Max. Tracking Speed	0 mm / sec

The Test and Post-Test Speeds are as low as the instrument will allow, to ensure a maximum number of data points captured. The Pre-Test speed is used only until the probe encounters the Trigger Force; *i.e.*, prior to contacting the tissue.

The Proportional, Integral, and Differential Gain are set to 0. These settings, when optimized, maintain the system at the Applied Force for the duration of the Contact Time. With soft tissue as a substrate, however, the probe and dosage form are constantly driven into the deformable surface. This results in visible damage to the tissue. Thus, the probe and dosage form are allowed to relax gradually from the Applied Force by setting these parameters to 0. The tracking speed, which is a measure of how rapidly the feedback is adjusted, is also set to 0.

The tissue on which the dosage forms are tested is secured in the Mucoadhesive Rig; the rig is then completely immersed in a 600 mL Pyrex beaker containing 375 mL of PBS. The tissue is maintained at approximately 37°C for the duration of the test; no stirring is used as the machine can detect the oscillations from the stir bar.

In the past, two classes of polymers have shown useful bioadhesive properties, hydrophilic polymers and hydrogels. In the large class of hydrophilic polymers, those containing carboxylic groups (*e.g.*, poly[acrylic acid]) exhibit the best bioadhesive properties. It is thus expected that polymers with the highest concentrations of carboxylic groups are preferred materials for bioadhesion on soft tissues. In other studies, the most promising polymers were sodium alginate, carboxymethylcellulose, hydroxymethylcellulose and methylcellulose. Some of these materials are water-soluble, while others are hydrogels.

Rapidly bioerodible polymers such as poly[lactide-co-glycolide], polyanhydrides, and polyorthoesters, whose carboxylic groups are exposed on the external surface as their smooth surface erodes, are particularly suitable for bioadhesive drug delivery systems. In addition, polymers containing labile bonds, such as polyanhydrides and polyesters, are well known for their hydrolytic reactivity. Their hydrolytic degradation rates can generally be altered by simple changes in the polymer backbone.

Representative natural polymers suitable for the present invention include proteins (*e.g.*, hydrophilic proteins), such as zein, modified zein, chitin, chitosan, casein, gelatin, gluten, serum albumin, or collagen, and polysaccharides such as cellulose, dextrans, polyhyaluronic acid, polymers of acrylic and methacrylic esters and alginic acid. These are generally less suitable for use in bioadhesive coatings due to higher levels of variability in the characteristics of the final products, as well as in degradation following administration.

Synthetically modified natural polymers include alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, and nitrocelluloses.

Representative synthetic polymers for use in bioadhesive coatings include polyphosphazines, poly(vinyl alcohols), polyamides, polycarbonates, polyalkylenes, polyacrylamides, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and copolymers thereof. Other polymers suitable for use in the invention include, but are not limited to, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly (ethylene terephthalate), poly(vinyl acetate), polyvinyl chloride, polystyrene, polyvinyl pyrrolidone, and polyvinylphenol. Representative bioerodible polymers for use in bioadhesive coatings include polylactides, polyglycolides and copolymers thereof, poly(ethylene terephthalate), poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), poly[lactide-co-glycolide], polyanhydrides (*e.g.*, poly(adipic anhydride)), polyorthoesters, blends and copolymers thereof.

Polyanhydrides are particularly suitable for use in bioadhesive delivery systems because, as hydrolysis proceeds, causing surface erosion, more and more carboxylic groups are exposed to the external surface. However, polylactides erode more slowly by bulk erosion, which is advantageous in applications where it is desirable to retain the bioadhesive coating for longer durations. In designing bioadhesive polymeric systems based on polylactides, polymers that have high concentrations of carboxylic acid are preferred. The high concentrations of carboxylic acids can be attained by using low molecular weight polymers (MW of 2000 or less), because low molecular weight polymers contain a high concentration of carboxylic acids at the end groups.

The polymers listed above can be obtained from sources such as Sigma Chemical Co., St. Louis, Mo., Polysciences, Warrenton, Pa., Aldrich, Milwaukee, Wis., Fluka, Ronkonkoma, N.Y., and BioRad, Richmond, Calif., or can alternatively be synthesized from

monomers obtained from these suppliers using standard techniques.

When the bioadhesive polymeric coating is a synthetic polymer coating, the synthetic polymer is typically selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends, and copolymers of thereof. Preferably, the synthetic polymer is poly(fumaric-co-sebacic) anhydride.

Another group of polymers suitable for use as bioadhesive polymeric coatings are polymers having a hydrophobic backbone with at least one hydrophobic group pendant from the backbone. Suitable hydrophobic groups are groups that are generally non-polar. Examples of such hydrophobic groups include alkyl, alkenyl and alkynyl groups. Preferably, the hydrophobic groups are selected to not interfere and instead to enhance the bioadhesiveness of the polymers.

A further group of polymers suitable for use as bioadhesive polymeric coatings are polymers having a hydrophobic backbone with at least one hydrophilic group pendant from the backbone. Suitable hydrophilic groups are groups that are capable of hydrogen bonding to another functional group. Example of such hydrophilic groups include negatively charged groups such as carboxylic acids, sulfonic acids and phosponic acids, positively charged groups such as (protonated) amines and neutral, polar groups such as amides and imines. Preferably, the hydrophilic groups are selected to not interfere and instead to enhance the bioadhesiveness of the polymers. The hydrophilic groups can be either directly attached to a hydrophobic polymer backbone or attached through a spacer group. Typically, a spacer group is an alkylene group, particularly a C_1-C_8 alkyl group such as a C_2-C_6 alkyl group. Preferred compounds containing one or more hydrophilic groups include amino acids (*e.g.*, phenyalanine, tyrosine and derivatives thereof) and amine-containing carbohydrates (sugars) such as glucosamine.

Polymers can be modified by increasing the number of carboxylic groups accessible during biodegradation, or on the polymer surface. The polymers can also be modified by binding amino groups to the polymer. The polymers can be modified using any of a number of different coupling chemistries available in the art to covalently attach ligand molecules with bioadhesive properties to the surface-exposed molecules of the polymeric microspheres.

The attachment of any positively charged ligand, such as polyethyleneimine or polylysine, to a polymer may improve bioadhesion due to the electrostatic attraction of the cationic groups coating the beads to the net negative charge of the mucus. The mucopolysaccharides and mucoproteins of the mucin layer, especially the sialic acid residues, are responsible for the negative charge coating. Any ligand with a high binding affinity for mucin could also be covalently linked to most polymers with the appropriate chemistry, such as with carbodiimidazole (CDI), and be expected to influence the binding to the gut. For example, polyclonal antibodies raised against components of mucin or else intact mucin, when covalently coupled to a polymer, would provide for increased bioadhesion. Similarly, antibodies directed against specific cell surface receptors exposed on the lumenal surface of the intestinal tract would increase the residence time when coupled to polymers using the appropriate chemistry. The ligand affinity need not be based only on electrostatic charge, but other useful physical parameters such as solubility in mucin or specific affinity to carbohydrate groups.

The covalent attachment of any of the natural components of mucin in either pure or partially purified form to the polymers would increase the solubility of the polymer in the mucin layer. The list of useful ligands would include but not be limited to the following: sialic acid, neuraminic acid, n-acetyl-neuraminic acid, n-glycolylneuraminic acid, 4-acetyl-n-acetylneuraminic acid, diacetyl-n-acetylneuraminic acid, glucuronic acid, iduronic acid, galactose, glucose, mannose, fucose, any of the partially purified fractions prepared by chemical treatment of naturally occurring mucin, *e.g.*, mucoproteins, mucopolysaccharides and mucopolysaccharide-protein complexes, and antibodies immunoreactive against proteins or sugar structure on the mucosal surface.

The attachment of polyamino acids containing extra pendant carboxylic acid side groups, such as polyaspartic acid and polyglutamic acid, may also increase bioadhesiveness. The polyamino chains would increase bioadhesion by means of chain entanglement in mucin strands as well as by increased carboxylic charge.

In certain embodiments, certain polymers suitable for the subject invention may be blended with catechol or a catechol derivative. Such polymers may be any non-biodegradable or biodegradable polymer. The polymers can be homopolymers or copolymers. The polymers that are copolymers can be block, alternating or random copolymers. The backbone of the bioadhesive polymer is preferably flexible in order to penetrate mucus and/or epithelial tissue. In the preferred embodiment, the polymer is a hydrophobic polymer. In certain embodiments,

the polymer is a biodegradable polymer and is used to form an oral dosage formulation.

Examples of biodegradable polymers suitable for use in the invention include synthetic polymers such as polyhydroxy acids, such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyesters, polyurethanes, poly(butyric acid), poly(valeric acid), poly(caprolactone), poly(hydroxybutyrate), poly(lactide-co-glycolide) and poly(lactide-co-caprolactone), and natural polymers such as alginate and other polysaccharides, collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein, modified zein, chitin, chitosan, and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo*, by surface or bulk erosion. The foregoing materials may be used alone, as physical mixtures (blends), or as co-polymers. In one aspect of the invention, a bioadhesive polymer is formed by first coupling a compound to a monomer and then polymerizing the coupled monomer. In this embodiment, the monomers are polymerized to form a polymer, including biodegradable and non-biodegradable polymers. Suitable polymers include, but are not limited to: polyanhydrides, polyamides, polycarbonates, polyalkylenes, polyalkylene oxides such as polyethylene glycol and poloxamers, polyalkylene terepthalates such as poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyethylene, polypropylene, poly(vinyl acetate), poly vinyl chloride, polystyrene, polyvinyl halides, polyvinylpyrrolidone, polyhydroxy acids, polysiloxanes, polyurethanes and copolymers thereof, modified celluloses, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, chitosan, chitin, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, and polyacrylates such as poly(methacrylate) poly(methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate) and poly(octadecyl acrylate).

The polymer backbone can be a known bioadhesive polymer that is hydrophilic or hydrophobic. Hydrophilic polymers include CARBOPOL™ (a high molecular weight,

crosslinked, acrylic acid-based polymers manufactured by NOVEON™), polycarbophil, pectin, carbomer, cellulose esters, and dextran.

In some embodiments, one can use non-biodegradable polymers, especially hydrophobic polymers. Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(meth)acrylic acid, copolymers of maleic anhydride with other unsaturated polymerizable monomers, poly(butadiene-co-maleic anhydride), polyamides, copolymers and mixtures thereof, and dextran, cellulose and derivatives thereof.

Hydrophobic polymers include polyanhydrides, poly(ortho)esters, and polyesters such as polycaprolactone. Typically, the polymer is sufficiently hydrophobic that it is not readily water soluble, for example, the polymer should be soluble up to less than about 1% w/w in water, preferably less than about 0.1% w/w in water, at room temperature or body temperature. In a preferred embodiment, the polymer comprises anhydride repeat units, *e.g.*, the polymer is a polyanhydride, such as a poly(anhydride-co-alkene). Particular examples of such polymers are polymers of maleic anhydrides, such as copolymers of maleic anhydride with alkenes (*e.g.*, poly(ethylene-co-maleic anhydride), poly(maleic anhydride-co-butadiene), poly(maleic anhydride-co-styrene). A copolymer can have more than two repeat units, such as poly(butadiene-co-styrene-co-maleic anhydride).

Others include poly(butadiene maleic anhydride) and other copolymers of maleic anhydrides.

Polyanhydrides can be formed from dicarboxylic acids as described in U.S. Patent No. 4,757,128 to Domb *et al.*, herein incorporated by reference. Suitable diacids include aliphatic dicarboxylic acids, aromatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acid, combinations of aromatic, aliphatic and aromatic-aliphatic dicarboxylic acids, aromatic and aliphatic heterocyclic dicarboxylic acids, and aromatic and aliphatic heterocyclic dicarboxylic acids in combination with aliphatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, and aromatic dicarboxylic acids of more than one phenyl group. Suitable monomers include sebacic acid (SA), fumaric acid (FA), bis(p-carboxyphenoxy)propane (CPP), isophthalic acid (IPh), and dodecanedioic acid (DD).

For materials in which the monomer or polymer has been modified, a wide range of molecular weights are suitable for the polymer that forms the backbone of the bioadhesive material. The molecular weight may be as low as about 200 Da (for oligomers) up to about 2,000 kDa. Preferably the polymer has a molecular weight of at least 1,000 Da, more preferably at least 2,000 Da, most preferably the polymer has a molecular weight of up to 20

kDa or up to 200 kDa. The molecular weight of the polymer may be up to 2,000 kDa. For polymers that are blended with catechol or a catechol derivative, the molecular weight is in the range of 20,000 to 1,000,000 Daltons, preferably 20,000 to 200,000 Daltons.

Polymers that are copolymers can be block, alternating or random copolymers, such as the maleic anhydride copolymer disclosed above.

Polymers can be crosslinked or uncrosslinked.

The backbone of bioadhesive polymers is advantageously sufficiently flexible to interpenetrate mucus and/or epithelial tissue, preferably both.

The range of substitution on the polymer backbone of a bioadhesive polymer varies greatly and depends on the polymer used and the desired bioadhesive strength.. For example, a butadiene-co-maleic anhydride copolymer that is 100% substituted with D-DOPA will have the same number of D-DOPA molecules per chain length as a 67% substituted ethylene-co-maleic anhydride copolymer. Typically, the polymer backbone has a percent substitution ranging from 1% to 100%, preferably greater than 5%, such as ranging from 5% to 75%.

The polymers that form the backbone of a bioadhesive polymer contain reactive functional groups that interact with the primary amino moiety of the compound.

Polymers used in blends preferably have functional groups that are not reactive with the compounds included in the compositions. The lack of reactivity can be absolute or can be lack of reactivity under the conditions to which the composition is exposed.

b. Reactive Functional Groups

For the polymers modified with a catechol functionality, it is important that the polymer or monomer that forms the polymeric backbone of a bioadhesive polymer contains accessible functional groups that easily react with the primary amino moieties contained in the compounds. Suitable reactive functional groups include aldehydes, ketones, carboxylic acid derivatives, anhydrides (*e.g.*, cyclic anhydrides), alkyl halides, acyl azides, isocyanates, isothiocyanates, and succinimidyl esters.

A polymer used in a blend (physical mixture) of the invention need not, and preferably does not, contain functional groups to react with a primary amino moiety.

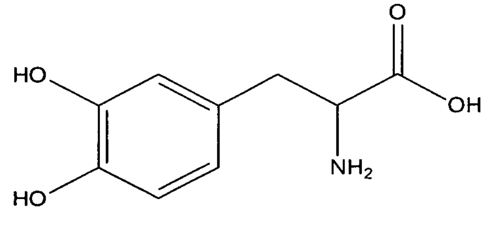
c. Sidechains containing Aromatic groups with one or more hydroxyl groups

Although this section is entitled "Sidechain Residue Compounds", implying the compounds are covalently attached to a polymer backbone, the compounds described herein are suitable both for attachment to a polymer backbone and for use in a blend (physical mixture), where no covalent bond exists between the polymer and the residue.

Aromatic groups containing one or more hydroxyl groups are attached to the polymeric backbone. The aromatic groups can be part of a compound that is grafted to the polymer backbone or the aromatic groups may be part of larger sidechains that are grafted to the polymer backbone. In one embodiment, the aromatic group containing one or more hydroxyl groups is catechol or a derivative thereof. Optionally the aromatic compound is a polyhydroxy aromatic compound, such as a trihydroxy aromatic compound (*e.g.* phloroglucinol and benserazide) or a multihydroxy aromatic compound (*e.g.* tannin). The aromatic moiety can also be an aromatic moiety that includes two or more (*e.g.*, three or more) hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, more typically, hydroxyl substituents or substituents hydrolyzable to hydroxyl substituents. A substituent hydrolyzable to a hydroxyl substituent is a substituent, which when cleaved by water (optionally mediated by an enzyme), that leaves a hydroxyl substituent attached to the phenyl ring. Common examples of such substituents include esters (-O-C(O)-R), carbamates (–O-C(O)-NRR') and carbonates (-O-C(O)-OR).

The catechol derivative also generally contains a reactive group, such as an amino, thiol, or halide group. Suitable sidechains which can be grafted to the polymer backbone include poly(amino acids), peptides, or proteins, having a molecular weight of 20 kDa or less, where at least 10% of the amino acids contain catechol residues; preferably, greater than 50%, more preferably 75%, and most preferably 100% of the amino acids contain catechol residues. Common amino acids with catechol-like residues are phenylanine, tyrosine and tryptophan. Additionally, synthetic amino acids that contain catechol residues may be prepared.

An exemplary catechol derivative is 3,4-dihydroxyphenylalanine (DOPA), which contains a primary amine. L-DOPA is known to be pharmaceutically active and is used as a treatment for Parkinson's disease. Tyrosine, the immediate precursor of DOPA, which differs only by the absence of one hydroxyl group in the aromatic ring, can also be used. Tyrosine is capable of conversion (*e.g.* by hydroxylation) to the DOPA form.



3,4-dihydroxyphenylalanine (DOPA)

In certain embodiments, the aromatic group is an amine-containing aromatic

compound, such as an amine-containing catechol derivative.

Certain of the sidechain residue compounds include a) an aromatic moiety comprising two or more hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, and b) a primary or secondary amino moiety.

A subgroup of these compounds is selected such that the cumulative amount of the compound converted to dopamine (*i.e.*, when the compound is not functionalized on (attached to) a polymer backbone) when infused into rat striatum is at least 65% less than for an equimolar amount of L-3,4-dihydroxyphenylalanine. In certain embodiments, the compounds used to form residues are selected such that the cumulative amount of the compound converted to dopamine when infused into rat striatum is at least 70%, 75%, 80%, 85%, 90%, 95% or 100% (*i.e.*, the compound is not converted to dopamine) less than an equimolar amount of L-3,4-dihydroxyphenylalanine. The cumulative amount of a compound converted to dopamine when infused into rat striatum can be measured according to the method described in Brannan, *et al.*, *Brain Res.* 718:165-168 (1996), the contents of which are incorporated herein by reference. Briefly, a microdialysis probe is lowered into the corpus striatum of anesthetized rats. The probe generally has a tip length of 3 mm and is perfused with an artificial cerebrospinal fluid solution. Concentrations of dopamine in the microdialysis samples are monitored at regular intervals by HPLC or another suitable analytical method. Once the dopamine concentration reaches a basal level, a 1 mM solution of a sidechain residue compound is perfused into the striatum via the probe, with continued monitoring of the dopamine concentration.

Separately or in addition to selection of sidechain residue compounds based upon their ability to be converted into dopamine, sidechain residue compounds can be selected such that the blood-brain barrier is substantially impermeable to these compounds when present as free molecules (*i.e.*, not covalently attached to a polymer). Typically, less than 10%, such as less than 5%, 4%, 3%, 2% or 1%, of a substantially impermeable compound is able to cross the blood-brain barrier. A suitable assay for determining permeability of the blood-brain barrier to a compound is described by Gomes and Soeares-da-Silva in *Brain Res.* 829:143-150 (1999), the contents of which are incorporated herein by reference. Briefly, the assay measures the uptake of a compound by immortalized rat capillary cerebral endothelial cells (RBE 4), which represent the blood-brain barrier. The endothelial cells are seeded in collagen-treated 24-well plastic culture clusters (16 mm internal diameter) at a density of 40,000 cells per well (20,000 cells/cm^2). For 24 hours prior to an experiment, the cell medium

is free of fetal bovine serum and basic fibroblast growth factor. Uptake experiments are typically performed 6 days after seeding. On the day of the experiment, the growth medium is aspirated and the cells are washed with Hanks' medium at 4 °C, followed by incubating the cells in Hanks' medium at 37 °C for 30 minutes. The cells are incubated for 6 minutes with 2 mL of 1 μM substrate (*e.g.*, sidechain residue compound) in Hanks' medium. Uptake is terminated by rapid removal of uptake solution with a vacuum pump connected to a Pasteur pipette, followed by a rapid wash with cold Hanks' medium and the addition of 250 μL of 0.2 mM perchloric acid. The acidified samples are stored under appropriate conditions until the substrate concentration is measured (*e.g.*, via HPLC).

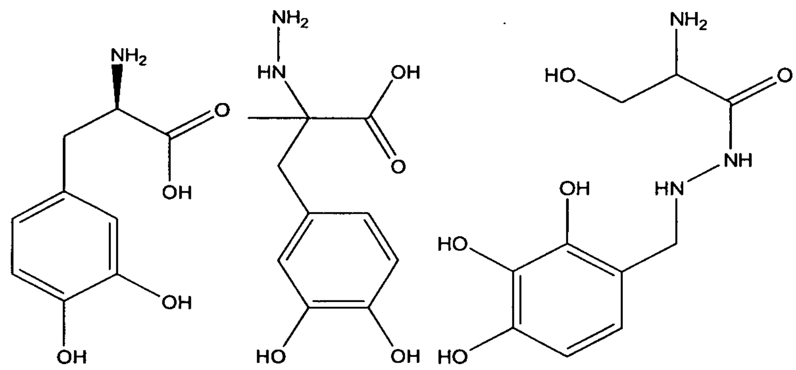
In another embodiment, the sidechain residue compounds include all sidechain residue compounds having the moieties discussed above, except L-DOPA and/or DL-DOPA.

Typically, the aromatic moiety is a monocyclic aromatic moiety that includes two or more hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, more typically, hydroxyl substituents or substituents hydrolyzable to hydroxyl substituents. Preferably, the aromatic moiety is a phenyl moiety that includes two or more (*e.g.*, three or more) hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, more typically, hydroxyl substituents or substituents hydrolyzable to hydroxyl substituents. An exemplary aromatic moiety is catechol. The aromatic moiety can include other substituents in addition to those indicated, but typically does not include additional substituents.

A substituent hydrolyzable to a hydroxyl substituent is a substituent, which when cleaved by water (optionally mediated by an enzyme), that leaves a hydroxyl substituent attached to the phenyl ring. Common examples of such substituents include esters (-O-C(O)-R) and carbonates (-O-C(O)-OR).

The primary or secondary amino moiety can be directly attached to a carbon atom or can be part of a hydrazinyl moiety (-NH-NHR).

Suitable compounds for forming residues include D-3,4-dihydroxyphenylalanine (D-DOPA), (D-, L- or a mixture thereof) carbidopa and (D-, L-, or a mixture thereof) benserazide, which have the following structures, respectively:



Other suitable compounds for forming residues include 3,4-dimethoxyphenyl-2-hydrazino-2-methyl propanoic acid, 2-aminocarbonyl-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid, 2-amino-3-(3,4-dimethoxyphenyl)-2-methyl hydrochloride, 2-amino-3-(3,4-dimethoxyphenyl)-2-methyl propane nitrile, methyl-DOPA, 3-O-methylcarbidopa and 4-O-methylcarbidopa, including enantiomers and mixtures thereof.

d. Blends containing a catechol or a catechol derivative

In one embodiment, the catechol or catechol derivative is blended with a biodegradable or non-biodegradable polymer to form a bioadhesive composition. The polymer is preferably a hydrophobic polymer. Suitable hydrophobic polymers include ethyl cellulose, poly(anhydrides), and polyesters. The preferred catechol derivative is 3,4-dihydroxyphenylalanine (DOPA), which contains a primary amine, or carbidopa. The catechol derivative can be present in an amount from about 0.5% to about 95% by weight of the polymer. For example, blending polycaprolactone with L-DOPA in a ratio of 2:1 w/w results in a bioadhesive material with an adhesive force of 491 mN/cm^2 compared to 50 mN/cm^2 for polycaprolactone alone.

II. Method of forming Bioadhesives

Two general methods are used to form the bioadhesive polymers of the invention. In one embodiment, one or more compounds are grafted onto a polymer backbone. Certain compounds used in this method are selected to have

a) an aromatic moiety comprising two or more hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, and

b) a primary or secondary amino moiety.

In this embodiment, the polymeric backbone is typically a non-biodegradable polymer. In a second embodiment, the compound is coupled to individual monomers and then polymerized.

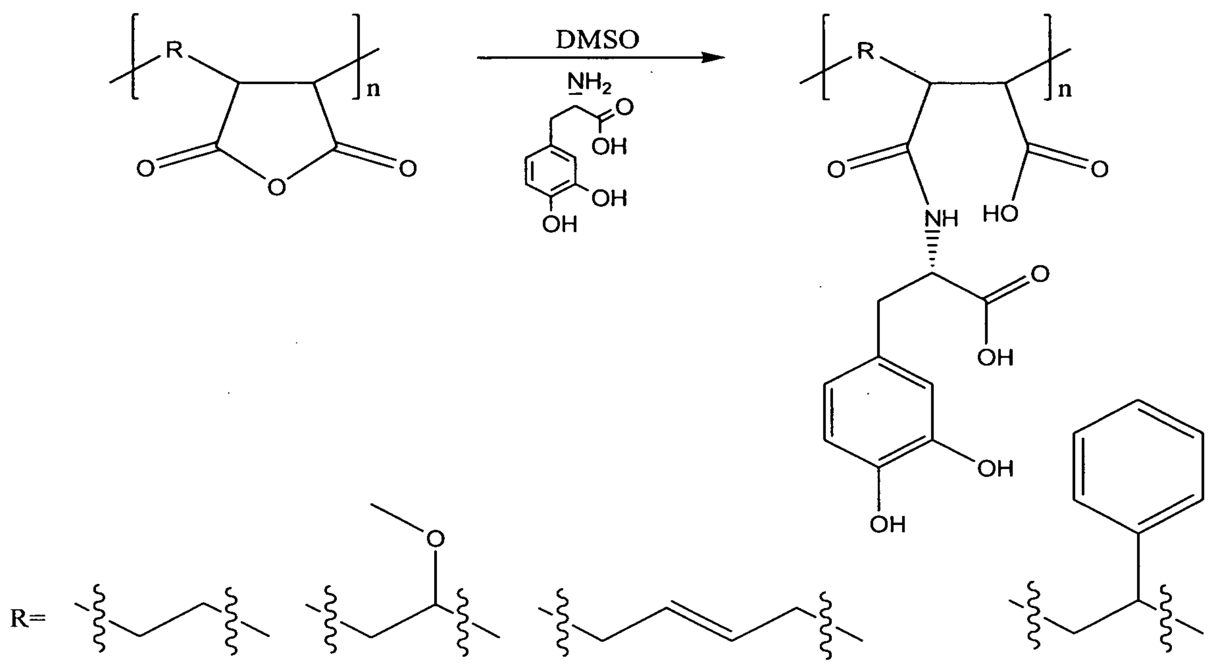
Chemistry which allows for the conjugation of a polymer or monomer to the compounds described above can be used. For example, the polymer or monomer is functionalized through a nucleophilic addition or a nucleophilic substitution reaction, including a Michael-type addition reaction, between the amino group in the compound and the polymer or monomer. Additionally, other procedures can be used in the coupling reaction. For example, carbodiimide and mixed anhydride based procedures form stable amide bonds between carboxylic acids or phosphates and amino groups, bifunctional aldehydes and bifunctional active esters react with primary amino groups, and divinylsulfone facilitates reactions with amino groups.

a. Polymer Grafting

The compounds are grafted onto the polymer backbone using standard techniques to form the bioadhesive polymer. An example of the grafting procedure is schematically depicted in Reaction 1, which depicts a nucleophilic substitution reaction between a primary amino moiety and a polymer. L-DOPA is grafted to maleic anhydride copolymers by reacting the free amine in L-DOPA with the maleic anhydride bond in the copolymer.

A variety of different polymers can be used as the backbone of the bioadhesive material. Representative polymers include random copolymers (*e.g.*, 1:1 copolymers) of maleic anhydride with ethylene, vinyl acetate, styrene, or butadiene. The variable portions of the backbone structures are designated as the R groups at the bottom of Reaction 1. In addition, a number of other compounds containing aromatic rings with hydroxy substituents, such as tyrosine or derivatives of catechol, can be used in reaction 1.

Reaction 1



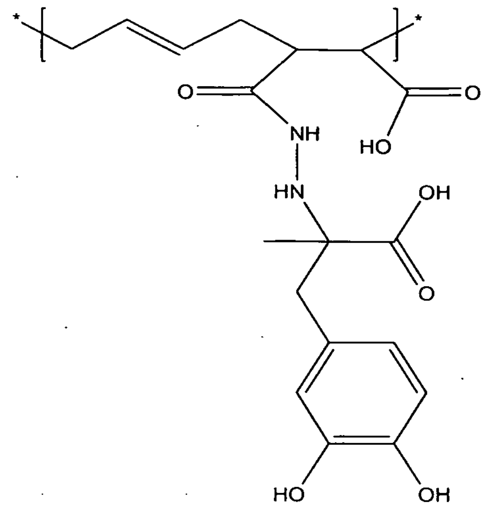
b. Polymer Synthesis

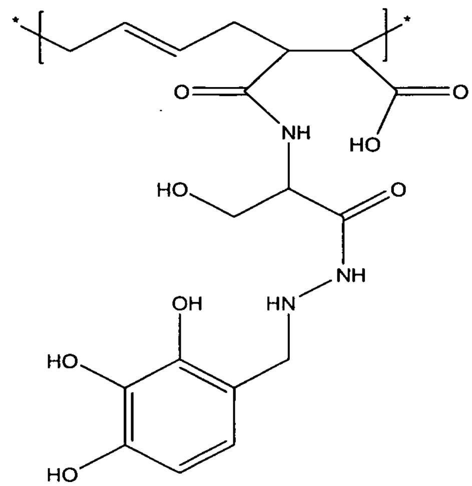
In another embodiment, the polymers are prepared by conjugate addition of one or more compounds containing a primary or secondary amine moiety to one or more monomers containing an amino reactive group. In one example, the monomer is an acrylate or a polymer acrylate. Particular monomers include a diacrylate such as 1,4-butanediol diacrylate; 1,3-propanediol diacrylate; 1,2-ethanediol diacrylate; 1,6-hexanediol diacrylate; 2,5-hexanediol diacrylate; and 1,3-propanediol diacrylate. In the coupling reaction, the monomer and the compound containing an aromatic group are each dissolved in an organic solvent (*e.g.*, tetrahydrofuran (THF), CH_2Cl_2, methanol (MeOH), ethanol (EtOH), $CHCl_3$, hexanes, toluene, benzene, CCl_4, glyme, diethyl ether, *etc.*) to form two solutions. The resulting solutions are combined, and the reaction mixture is heated to yield the desired polymer. The molecular weight of the synthesized polymer can be determined by the reaction conditions (*e.g.*, temperature, starting materials, concentration, solvent, *etc*) used in the synthesis.

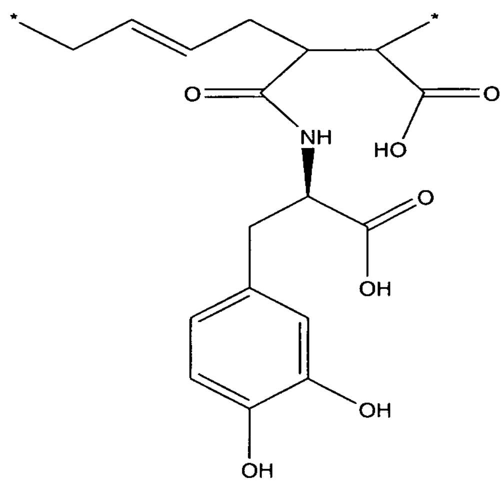
In one example, a monomer, such as 1,4-phenylene diacrylate or 1,4 butanediol diacrylate having a concentration of 1.6 M, and D-DOPA or another primary amine containing aromatic molecule are each dissolved in an aprotic solvent such as dimethylformamide (DMF) or dimethylsulfoxide (DMSO) to form two solutions, the

solutions are mixed in a 1:1 molar ratio between the diacrylate and the amine group and heated to 56 °C to form a bioadhesive material.

Exemplary polymers prepared by this method include one or more of the following repeat units, including combinations thereof:







c. **Blends**

Bioadhesive compositions of the invention also include blends, which include a polymer and one or more of the compounds identified as suitable sidechain residues above. However, unlike the bioadhesive polymers of the invention, there is typically no covalent bond formed between the sidechain residue compound and the polymer in the bioadhesive compositions (*i.e.*, the polymer does not chemically react with the compound, although hydrogen bonds, ionic bonds and/or van der Waals interactions can occur).

In one embodiment, the sidechain residue compound is not carbidopa. In another

embodiment, when the sidechain residue compound is carbidopa, the blend comprises an active agent that is not carbidopa or L-DOPA.

Suitable polymers for use in blends are described above. Typically, the polymer itself is not bioadhesive, but the polymer can be bioadhesive (*e.g.*, a polymer with hydrogen bond-forming pendant groups). Preferably, the polymer is a hydrophobic polymer such as a poly(lactone) (*e.g.*, poly(caprolactone), a polyester or a hydrophobic cellulose (*e.g.*, ethyl cellulose)).

To form the blends of the invention, typically a polymer and one or more sidechain residue compounds are dissolved in a compatible solvent and blended together, such as under an adhesive force of at least 10 mN/cm^2, at least 25 mN/cm^2, at least 50 mN/cm^2 or at least 100 mN/cm^2 (*e.g.*, 10-500 mN/cm^2, 25-100 mN/cm^2). The solvent is then evaporated, preferably at a controlled temperature and rate of removal. Alternatively or in combination with general evaporation, the blend can be spray dried or dried at room temperature.

In another example, a mixture of a polymer and one or more sidechain residue compounds are melted at or slightly above the melting point of the polymer, typically while being mixed. Both the polymer and sidechain residue compound should be selected such that they are chemically stable (*e.g.*, do not decompose, do not oxidized) at the melting point temperature. After the composition has re-solidified, it can be milled in order to obtain particles of the desired size.

In certain examples, blends can be prepared by dry mixing of a polymer and one or more sidechain residue compounds, provided that the sidechain residue compound is sufficiently distributed throughout the blend. The sufficiency of distribution can be assessed by measuring the bioadhesiveness of the blend; a blend of the invention having a sufficient distribution of sidechain residue compounds has adhesion of at least 10 N/m^2.

Blends of a biodegradable or non-degradable polymer with a catechol or catechol derivative can be prepared by mixing, such as by dissolving the polymer and the catechol or catechol derivative in a suitable solvent and then removing the solvent under controlled conditions of temperature and rate of solvent removal. The resulting blends can be spray dried or dried at room temperature. Alternatively, the blend can be prepared by melt blending the polymer and the catechol or catechol derivative at a temperature corresponding to the melting point of the polymer. For example, polycaprolactone can be melt-blended with L-DOPA (m.p. 295°C) at a temperature of 58-60°C, which corresponds to the meting point of polycaprolactone. The blends can be also coated onto a substrate using melt extrusion, a

fluidized bed, or any method of coating known in the art. The catechol or catechol derivative is present in amount from about 0.5% to about 95% by weight of the polymer.

In each of the above methods, additional components can be added to the mixture prior to dissolution, melting and/or mixing. However, the additional components should be stable under the conditions the mixture is exposed to. In particular, active agents should be stable at the melting point temperature if that method is employed.

The weight ratio of polymer to sidechain residue compound in a blend can be selected to give the desired amount of bioadhesion. Typically, the weight ratio of sidechain residue compound to polymer is 0.5% to 95% by weight, such as 5% to 75% or 25% to 75%.

III. Method for Stabilizing Bioadhesives

The invention includes a bioadhesive material comprising one of the bioadhesive polymers or polymer blends (often referred to collectively hereinbelow as "bioadhesive polymers") described herein and an additive that stabilizes the polymeric component from erosion, dissolution or both, where at least 50% by weight of a 1 mm thick film of the bioadhesive material remains, *e.g.*, after 12 hours in a buffered pH 4.5 dissolution bath.

In certain embodiments, the bioadhesive material film is exposed to the dissolution bath for 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 24 hours or longer. In certain such embodiments, the amount of bioadhesive material film remaining after exposure to the dissolution bath is at least 50% by weight, at least 60% by weight, at least 70% by weight, at least 80% by weight, at least 90% by weight, at least 95% by weight, at least 97% by weight, at least 98% by weight or even at least 99% by weight of the polymer prior to exposure. A suitable dissolution bath, a USP II apparatus, is described below in the Examples. In certain embodiments, the dissolution bath is stirred at 50 rpm and the temperature is 37° C.

In certain embodiments, the bioadhesive polymers are stabilized against erosion by incorporating one or more additives selected from (1) polyanhydrides, such as those having a molecular weight average in excess of 20,000, (2) acidic components (including precursors thereof), (3) metal compounds, (4) stabilizing polymers, and (5) hydrophobic components.

a. Polyanhydrides

Suitable polyanhydrides for stabilizing the bioadhesive polymers discussed above are described in U.S. Patent No. 4,757,128 to Domb *et al.* and U.S. Patent No. 5,955,096 to Mathiowitz *et al.*, the contents of which are incorporated herein by reference. Polymers may be synthesized from highly pure isolated prepolymers formed from: aliphatic dicarboxylic

acids, aromatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, combinations of aromatic, aliphatic and aromatic-aliphatic dicarboxylic acids, aromatic and aliphatic heterocyclic dicarboxylic acids and aromatic and aliphatic heterocyclic dicarboxylic acids in combination with aliphatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, and aromatic dicarboxylic acids of more than one phenyl group. For example, the following monomers are suitable for synthesizing bioadhesive copolymers: bis(p-carboxyphenoxy)alkanes; hydroquinone-O,O' diacetic acid; 1,4-bis-carboxymethyl benzene; 2,2-bis(4-hydroxphenyl)propane-O,O'-diacetic acid; 2,2-bis(4-carboxyphenyl)propane; terephthalic acid; bis(4-carboxyphenyl)alkanes; 1,4-phenylene dipropionic acid; cyclohexane dicarboxylic acids, adipic acid, sebacic acid (SA), bis(p-carboxyphenoxy)propane (CPP), isophthalic acid (IPh), and dodecanedioic acid (DD). A particular polyanhydride is poly(fumaric acid-co-sebacic acid) (pFA:SA) (*e.g.*, a 20:80 copolymer of p(FA:SA)). Another particular polyanhydride is polyadipic anhydride.

As used herein, the term "anhydride oligomer" refers to a diacid or polydiacid linked by anhydride bonds, and having carboxy end groups linked to a monoacid such as acetic acid by anhydride bonds. The anhydride oligomers have a molecular weight less than about 5000, typically between about 100 and 5000 daltons, or are defined as including between one to about 20 diacid units linked by anhydride bonds. The anhydride oligomer is hydrolytically labile. As analyzed by gel permeation chromatography, the molecular weight may be, for example, on the order of 200-400 for fumaric acid oligomer (FAPP) and 2000-4000 for sebacic acid oligomer (SAPP). In one embodiment, the diacids are those normally found in the Krebs glycolysis cycle. The anhydride oligomer compounds preferably have high chemical reactivity.

Anhydride oligomers can be incorporated into a polyanhydride by combining a finely ground dispersion of particles of oligomer in a solution or dispersion with the polyanhydride. Alternatively, the oligomer compound can be incorporated into the polymer by dispersing the polyanhydride in a solution or dispersion of the oligomer compound and then removing the solvent by evaporation or filtration.

While Applicants do not wish to be bound by theory, it is believed that free carboxylic acid groups of the polyanhydrides form hydrogen bonds with hydroxyl group in the polymers functionalized or blended with catechol and derivatives thereof and/or create a local acidic environment, thereby stabilizing the polymers. It is also believed that the erosion of polyanhydrides is less affected by pH than the polymers functionalized or blended with

catechol or a derivative, such that a polyanhydride selected for use herein advantageously erodes at a largely pH-independent rate and/or erodes slowly upon hydration.

Typically, the amount of polyanhydride added to a bioadhesive polymer is from about 0.5% to about 75% by weight, preferably about 5% to about 50% and more preferably about 10% to about 25%.

b. Acidic Components

The bioadhesive polymers can additionally be stabilized by the incorporation of a small molecule (*i.e.*, non-polymeric or oligomeric) acidic component, preferably a slow release acidic component. Typically, the acid is a weak organic acid, for example, an acid having a pKa of about 1 to about 7, such as about 1 to about 5.5, typically about 1.2 to 4.5. Preferably, the acid is poorly soluble in water as defined in the USP, but miscible with the bioadhesive polymer. The acid may contain one or more carboxylic, phosphonic, phosphoric, sulfonic, sulfinic or sulfenic acid moieties, preferably two or more acid moieties. Typically, the acid contains two or more carboxylic acid moieties. Exemplary acids include succinic acid, fumaric acid, citric acid, sebacic acid, adipic acid, lactic acid, malic acid, ascorbic acid, tartaric acid and sorbic acid. In certain embodiments, the acid is not citric acid. In certain such embodiments, the acid is not citric acid, fumaric acid, sebacic acid or lactic acid. In other embodiments, the acid is not a sugar. A combination of two or more such acids may be incorporated into a polymer.

The acid may be an acid precursor, such as an anhydride. An acid precursor is a molecule that is hydrolyzed or metabolized into an acid. Suitable anhydrides includes symmetrical anhydrides (*e.g.*, acetic anhydride, cyclohexanecarboxylic anhydride, hexanoic anhydride, chloroacetic anhydride, thiobenzoic anhydride, thiopropionic anhydride, 2-chloroethanesulfinic anhydride, benzenesulfonic anhydride and cyclic anhydrides formed from two acid groups attached to the same molecule such as succinic anhydride, cyclohexane-1,2,3,4-tetracarboxylic acid 3,4-anhydride and phthalic anhydride), unsymmetrical (mixed) anhydrides (*e.g.*, acetic propionic anhydride, benzoic thioacetic anhydride, acetic chloroacetic anhydride, benzenesulfinic ethanesulfonic anhydride, chloroacetic-4-nitrobenzenesulfonic anhydride) and chalcogen analogues of anhydrides (*e.g.*, benzoic thioanhydride, 4-chlorocyclohexane-1-carbothioic thioanhydride, acetic propionic thioanhydride, acetic thiopropionic anhydride, propionic thioacetic anhydride, acetic thiopropionic thioanhydride, propionic thioacetic thioanhydride, thioacetic thiopropionic anhydride). Preferably, the anhydride is succinic anhydride, phthalic anhydride, maleic anhydride, adipic anhydride,

butyric anhydride, isobutyric anhydride, propionic anhydride or another carboxylic acid anhydride. More preferably, the anhydride is succinic anhydride.

The acids advantageously are present in a bioadhesive polymer for an extended period of time (*e.g.*, not washed away in an aqueous environment), which is typically achieved either by virtue of low water solubility or by virtue of coating the acids with an appropriate coating. Such acids are collectively referred to herein as slow-release acid components. Acids selected on the basis of solubility typically have a solubility in water of less than 10 mg/mL at pH 4.5 and below. Coatings for an acid are selected such that they do not appreciably dissolve at pH 4.5 or below or such that they coat the acid until the formulation (*i.e.*, polymer) into which the coated acid is incorporated has passed through the stomach (*e.g.*, an enteric coating).

Typically, the amount of an acidic component (including acid precursors) added to a bioadhesive polymer is from about 0.5% to about 75% by weight, such as about 1% to about 65%, preferably about 5% to about 50% (about 5% to about 45%, about 10% to about 30%) and more preferably about 10% to about 25%.

c. Metal Compounds

The bioadhesive polymers described above can also be stabilized by the incorporation of a metal compound, as described in U.S. Patent No. 5,985,312 to Jacob *et al.*

The metal compounds preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and hydroxides, including oxides of calcium, iron, copper and zinc. The metal compounds can be combined with a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers.

Metal compounds which can be incorporated into polymers preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and metal hydroxides, which are capable of becoming combined with a polymer to thereby improve the bioadhesiveness of the polymer. As defined herein, a water-insoluble metal compound is defined as a metal compound with little or no solubility in water, for example, less than about 0.0 to 0.9 mg/ml.

The water-insoluble metal compounds can be derived from a wide variety of metals, including, but not limited to, calcium, iron, copper, zinc, cadmium, zirconium and titanium. The water insoluble metal compound preferably is a metal oxide or hydroxide. Water insoluble metal compounds of multivalent metals are preferred. Representative metal oxides suitable for use in the compositions described herein include cobalt oxide (I) (CoO), cobalt

oxide (II)(Co_2O_3), selenium oxide (SeO_2), chromium double oxide (CrO_2), manganese oxide (MnO_2), titanium oxide (TiO_2), lanthanum oxide (La_2O_3), zirconium oxide (ZrO_2), silicon oxide (SiO_2), scandium oxide (Sc_2O_3), beryllium oxide (BeO), tantalum oxide (Ta_2O_5), cerium oxide (CeO_2), neodymium oxide (Nd_2O_3), vanadium oxide (V_2O_5), molybdenum oxide (Mo_2O_3), tungsten oxide (WO), tungsten trioxide (WO_3), samarium oxide (Sm_2O_3), europium oxide (Eu_2O_3), gadolinium oxide (Gd_2O_3), terbium oxide (Tb_4O_7), dysprosium oxide (Dy_2O_3), holmium oxide (Ho_2O_3), erbium oxide (Er_2O_3), thulium oxide (Tm_2O_3), ytterbium oxide (Yb_2O_3), lutetium oxide (Lu_2O_3), aluminum oxide (Al_2O_3), indium oxide (InO_3), germanium oxide (GeO_2), antimony oxide (Sb_2O_3), tellurium oxide (TeO_2), nickel oxide (NiO), and zinc oxide (ZnO). Other oxides include barium oxide (BaO), calcium oxide (CaO), nickel oxide (III) (Ni_2O_3), magnesium oxide (MgO), iron oxide (II) (FeO), iron oxide (III) (Fe_2O_3), copper oxide (II) (CuO), cadmium oxide (CdO), and zirconium oxide (ZrO_2). In certain embodiments, the metal compound is ferric oxide, copper oxide or zinc oxide or a combination thereof. In other embodiments, the metal compound is a zirconate, such as magnesium zirconate or calcium zirconate. In yet other embodiments, the metal compound is a silicate, such as magnesium silicate (*e.g.*, a hydrated magnesium silicate such as talc) or calcium silicate. Advantageously, metal compounds which are incorporated into polymers are metal compounds which are already approved by the FDA or an equivalent agency as either food or pharmaceutical additives, such as zinc oxide or talc.

The water-insoluble metal compounds can be incorporated into a polymer by, for example, one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; and (d) coating techniques such as fluidized bed, pan coating, or any similar methods known to those skilled in the art, which produce a metal compound enriched layer on the surface of the device. In one embodiment, nanoparticles or microparticles of the water-insoluble metal compound are incorporated into the polymer, preferably as a uniform dispersion.

Fine metal oxide particles can be produced, for example, by micronizing a metal oxide by mortar and pestle treatment to produce particles ranging in size, for example, from 10.0 to 300 nm. The metal oxide particles can be incorporated into a polymer, for example, by dissolving or dispersing the particles into a solution or dispersion of the polymer.

Metal compounds are optionally coated with a protective coating, such as an enteric

coating or a rate controlling coating. Such coatings are selected in order to release the metal compound only when the system is exposed to gastric fluid or another targeted environment.

Typically, the amount of a metal compound added to a bioadhesive polymer is from about 1% to about 65% by weight, preferably about 5% to about 45% and more preferably about 10% to about 30%.

d. Stabilizing Polymers

The bioadhesive polymers described above can also be stabilized by the incorporation of certain polymers, particularly a hydrophilic polymer (hydrogel) that forms a rigid gel at pH 4.5 and higher or a hydrophobic polymer. Preferably, a hydrogel has little or no swelling at pH 4.5 or less. One group of suitable polymers includes polymers with pendant hydroxyl, carboxylic acid, amine, amide and/or urea moieties (or, more generally, hydrogen bond donors and/or acceptors). Specific examples of stabilizing polymers include polyvinyl alcohol, polyacrylamide, polyacrylonitrile, polymethacrylic acid, polyacrylic acid (*e.g.*, Carbomer), alginate (*e.g.*, sodium alginate), chitin, chitosan, zein and shellac. Typically, the hydrogel is Carbomer or an alginate. In certain embodiments, the stabilizing polymer is not an alginate. In certain embodiments, the stabilizing polymer is not ethyl cellulose, cellulose acetate and/or zein.

Stabilizing polymers can be combined with a bioadhesive polymer by combining a finely ground dispersion of particles in a solution or dispersion with the bioadhesive polymer. Alternatively, the stabilizing polymer can be combined with the bioadhesive polymer by dispersing the bioadhesive polymer in a solution or dispersion of the hydrogel and then removing the solvent by evaporation or filtration.

Typically, the amount of a stabilizing polymer added to a bioadhesive polymer is from about 1% to about 90% by weight, preferably about 5% to about 70% and more preferably about 10% to about 50%.

e. Hydrophobic Components

The bioadhesive polymers described above can also be stabilized by combination with one or more hydrophobic components. Examples of hydrophobic small molecules include waxy materials (*e.g.*, carnauba wax, beeswax, Chinese wax, spermaceti, lanolin, bayberry wax, Candelilla wax, castor wax, esparto wax, Japan wax, jojoba oil, ouricury wax, rice bran wax, ceresin waxes, montan wax, ozocerite, peat waxes, paraffin wax, polyethylene waxes) and polyglycerol fatty acid esters.

Typically, the amount of a hydrophobic component added to a bioadhesive polymer is

from about 1% to about 25% by weight, preferably about 2% to about 10%.

f. Combinations of Additives

The stability of bioadhesive polymers can also be enhanced by incorporating materials from two or more of the classes of materials described above. Thus, the invention includes combinations including: (1) a polyanhydride and an acidic component, (2) a polyanhydride and a metal compound, (3) a polyanhydride and a stabilizing polymer, (4) a polyanhydride and a hydrophobic component, (5) an acidic component and a metal compound, (6) an acidic component and a stabilizing polymer, (7) an acidic component and a hydrophobic component, (8) a metal compound and a stabilizing polymer, (9) a metal compound and a hydrophobic component, (10) a stabilizing polymer and a hydrophobic component, (11) a polyanhydride and an acidic component and a metal compound, (12) a polyanhydride and an acidic component and a stabilizing polymer, (13) a polyanhydride and an acidic component and a hydrophobic component, (14) a polyanhydride and a metal compound and a stabilizing polymer, (15) a polyanhydride and a metal compound and a hydrophobic component, (16) a polyanhydride and a stabilizing polymer and a hydrophobic component, (17) an acidic component and a metal compound and a stabilizing polymer, (18) an acidic component and a metal compound and a hydrophobic component, (19) an acidic component and a stabilizing polymer and a hydrophobic component, (20) a metal compound and a stabilizing polymer and a hydrophobic component, (21) a polyanhydride and an acidic component and a metal compound and a stabilizing polymer, (22) a polyanhydride and an acidic component and a metal compound and a hydrophobic component, (23) a polyanhydride and a metal compound and a stabilizing polymer and a hydrophobic component, (24) an acidic component and a metal compound and a stabilizing polymer and a hydrophobic component and (25) at least one material from each of the five categories. In a one embodiment, a combination of an acidic component and a hydrophobic component are incorporated into a bioadhesive polymer, particularly citric acid and ethylcellulose.

The proportion of additives, when there is a combination of additives, typically falls within the ranges for the individual classes of additives disclosed above.

IV. Applications for Bioadhesives

Bioadhesive materials described herein may be used in a wide variety of drug delivery, tissue engineering and other medical and diagnostic applications. Bioadhesive materials may be formed into microparticles, such as microspheres or microcapsules, or may be a coating on such microparticles. The bioadhesive materials may be applied to tissue

engineering matrices or medical implants. In the preferred embodiment, the material is applied as a coating to a solid oral dosage formulation, such as a tablet, capsule, drug eluting device or multiparticulates. The coating may be applied by direct compression or by applying a solution containing the material to the tablets or capsules. In one embodiment, the bioadhesive material is in the matrix of a tablet or other drug delivery device. Optionally, the tablet or drug delivery device contains a coating, such as a coating containing the bioadhesive material or another bioadhesive polymer or an enteric coating.

Bioadhesive materials used as coatings preferably do not appreciably swell upon hydration, such that they do not substantially inhibit or block movement (*e.g.*, of ingested food) through the gastrointestinal tract, as compared to the polymers disclosed by Duchene *et al.* Generally, polymers that do not appreciably swell upon hydration include one or more hydrophobic regions, such as a polymethylene region (*e.g.*, $(CH_2)_n$, where n is 4 or greater). The swelling of a polymer can be assessed by measuring the change in volume when the polymer is exposed to an aqueous solution. Polymers that do not appreciably swell upon hydration expand in volume by 50% or less when fully hydrated. Preferably, such polymers expand in volume by less than 25%, less than 20%, less than 15%, less than 10% or less than 5%. A polymer that does not appreciably swell upon hydration can be mixed with a polymer that does swell (*e.g.*, Carbopol™, poly(acrylic acid), provided that the amount of swelling in the polymer does not substantially interfere with bioadhesiveness.

In one embodiment, the bioadhesive coating consists of two layers, an inner bioadhesive layer that does not substantially swell upon hydration and an outer bioadhesive layer that is readily hydratable and optionally bioerodable, such as one comprised of CARBOPOL™.

A tablet or a drug eluting device can have one or more coatings in addition to the bioadhesive coating. These coatings and their thickness can, for example, be used to control where in the gastrointestinal tract the bioadhesive coating becomes exposed. In one example, the additional coating prevents the bioadhesive coating from contacting the mouth or esophagus. In another example, the additional coating remains intact until reaching the small intestine.

Examples of coatings include methylmethacrylates, zein, modified zein, chitin, chitosan, cellulose acetate, cellulose phthalate, HPMC, sugars, enteric polymers, gelatin and shellac. Premature dissolution of a tablet in the mouth can be prevented with hydrophilic polymers such as HPMC or gelatin.

Coatings used in tablets of the invention, typically include a pore former, such that the coating is permeable to the drug.

Tablets, capsules and drug eluting devices of the invention can be coated by a wide variety of methods. Suitable methods include compression coating, coating in a fluidized bed or a pan, hot melt (extrusion) coating and enrobing. Such methods are well known to those skilled in the art.

In one embodiment, the bioadhesive material is used in drug depot or reservoir systems, such as an osmotic drug delivery system. In one aspect of this embodiment, the bioadhesive material is present in a matrix surrounding the drug to be delivered and/or as a coating on the surface of the system. The depot or reservoir systems contain a microporous or macroporous membrane that separates the outside environment from the drug inside the system. The osmotic delivery system contains osmotic agents, which bring water into the system, causing a swellable material, such as a polymeric matrix or separate polymeric layer, to swell. When the material inside the system swells, it pushes the drug against the semi-permeable membrane and out of the system.

The bioadhesive coating adheres to the mucosa in the aqueous environment of the gastrointestinal tract. As a result, the bioavailability of therapeutic agents is enhanced through increased residence time at the target absorption rate. Typically, the solid oral dosage form contains rate controlling agents, such as hydroxypropylmethyl cellulose (HPMC) and microcrystalline cellulose (MCC). Optionally, the drug may be in the form or microparticles or nanoparticles. In one embodiment, a tablet contains a core containing a nanoparticulate drug and enhancers in a central matrix of rate controlling agents, such as hydroxypropylmethyl cellulose (HPMC) and microcrystalline cellulose (MCC). The core is surrounded on its circumference by bioadhesive polymer or composition of the invention. Optionally, the final tablet is coated with an enteric coating, such as Eudragit L100-55, to prevent release of the drug until the tablet has moved to the small intestine.

The bioadhesive materials may be used in or as a coating on prosthetics, such as dental prosthetics. The materials may be used as dental adhesives, or bone cements and glues. The materials are suitable for use in wound healing applications, such as synthetic skins, wound dressings, and skin plasters and films.

In order to alter the physical properties of bioadhesive materials, additional components can be added to a composition. Such components include bioadhesive modifiers, solvents, thermoplastic polymers and plasticizers.

Bioadhesive materials can be mixed with one or more plasticizers or thermoplastic polymers. Such agents typically increase the strength and/or reduce the brittleness of polymeric coatings. Plasticizers can be hydrophobic or hydrophilic. Examples of plasticizers include dibutyl sebacate, polyethylene glycol, triethyl citrate, dibutyl adipate, dibutyl fumarate, diethyl phthalate, ethylene oxide-propylene oxide block copolymers such as Pluronic™ F68 and di(sec-butyl) fumarate. Example of thermoplastic polymers include polyesters, poly(caprolactone), polylactide, poly(lactide-co- glycolide), methyl methacrylate (*e.g.*, EUDRAGIT™), cellulose and derivatives thereof such as ethyl cellulose, cellulose acetate and hydroxypropyl methyl cellulose (HPMC) and large molecular weight polyanhydrides. The plasticizers and/or thermoplastic polymers are mixed with a bioadhesive polymer to achieve the desired properties. Typically, the proportion of plasticizers and thermoplastic polymers, when present, is from 0.5% to 50% by weight.

Bioadhesive modifiers include both natural and synthetic bioadhesive modifiers, which can be swellable or non-swellable and gellable or non-gellable. Swellable modifiers include fluid-imbibing displacement polymers (osmopolymers), such as poly(alkylene oxide), hydrogels (CARBOPOL®), polyacrylamide, crosslinked poly(indene-co-maleic anhydride), poly(acrylic acid), polysaccharides and polyglucan.

Gellable or non-gellable modifiers include karaya gum, guar gum, okra gum, gum arabic, acacia gum, pectina gum, ghatti gum, tragacanth gum, xanthan gum, locust bean gum, psyllium seed gum, tamarind gum, destria gum, casein gum and other gums.

Natural bioadhesive modifiers include cellulose compounds (cellulose, ethylcellulose, methylcellulose, nitrocellulose, propylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, carboxymethylcellulose and hydroxypropylmethylcellulose, including alkyl and hydroxyalkyl derivatives), karaya gum, prolamines (zein), L-DOPA, benserazide, carbidopa, dopamine, 3-O-methyldopa and other L-DOPA metabolites. In certain embodiments, the natural bioadhesive modifiers exclude L-DOPA and/or its metabolites.

The bioadhesive modifiers can, for example, be blended with the bioadhesive materials of the invention during the preparation of a pharmaceutical composition. For tablets, a bioadhesive modifier is generally blended with a bioadhesive material though dry or wet mixing prior to tablet preparation.

As disclosed in U.S. Patent Nos. 5,985,312, 6,123,965 and 6,368,586, the contents of which are incorporated herein by reference, bioadhesive polymers and compositions, such as those named above, having a metal compound combined therewith have a further improved

ability to adhere to tissue surfaces, such as mucosal membranes. The metal compound combined with the polymer can be, for example, a water-insoluble metal oxide. The combination of metal compounds with a wide range of different polymers, even those that are not normally bioadhesive, improves their ability to adhere to tissue surfaces such as mucosal membranes.

Metal compounds which can be incorporated into polymers to improve their bioadhesive properties preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and metal hydroxides, which are capable of becoming incorporated into and associated with a polymer to thereby improve the bioadhesiveness of the polymer. As defined herein, a water-insoluble metal compound is defined as a metal compound with little or no solubility in water, for example, less than about 0.0 to 0.9 mg/ml.

The water-insoluble metal compounds can be derived from a wide variety of metals, including, but not limited to, calcium, iron, copper, zinc, cadmium, zirconium and titanium. The water insoluble metal compound preferably is a metal oxide or hydroxide. Water insoluble metal compounds of multivalent metals are preferred. Representative metal oxides suitable for use in the compositions described herein include cobalt (I) oxide (CoO), cobalt (II) oxide (Co_2O_3), selenium oxide (SeO_2), chromium (IV) oxide (CrO_2), manganese oxide (MnO_2), titanium oxide (TiO_2), lanthanum oxide (La_2O_3), zirconium oxide (ZrO_2), silicon oxide (SiO_2), scandium oxide (Sc_2O_3), beryllium oxide (BeO), tantalum oxide (Ta_2O_5), cerium oxide (CeO_2), neodymium oxide (Nd_2O_3), vanadium oxide (V_2O_5), molybdenum oxide (Mo_2O_3), tungsten oxide (WO), tungsten trioxide (WO_3), samarium oxide (Sm_2O_3), europium oxide (Eu_2O_3), gadolinium oxide (Gd_2O_3), terbium oxide (Tb_4O_7), dysprosium oxide (Dy_2O_3), holmium oxide (Ho_2O_3), erbium oxide (Er_2O_3), thulium oxide (Tm_2O_3), ytterbium oxide (Yb_2O_3), lutetium oxide (Lu_2O_3), aluminum oxide (Al_2O_3), indium oxide (InO_3), germanium oxide (GeO_2), antimony oxide (Sb_2O_3), tellurium oxide (TeO_2), nickel oxide (NiO), and zinc oxide (ZnO). Other oxides include barium oxide (BaO), calcium oxide (CaO), nickel oxide (III) (Ni_2O_3), magnesium oxide (MgO), iron (II) oxide (FeO), iron (III) oxide (Fe_2O_3), copper oxide (II) (CuO), cadmium oxide (CdO), and zirconium oxide (ZrO_2).

Preferred properties defining the metal compound include: (a) substantial insolubility in aqueous environments, such as acidic or basic aqueous environments (such as those present in the gastric lumen); and (b) ionizable surface charge at the pH of the aqueous environment.

The water-insoluble metal compounds can be incorporated into the material by one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal

compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; and (d) coating techniques such as fluidized bed, pan coating, or any similar methods known to those skilled in the art, which produce a metal compound enriched layer on the surface of the device. In one embodiment, nanoparticles or microparticles of the water-insoluble metal compound are incorporated into the polymer.

Advantageously, metal compounds which are incorporated into materials to improve their bioadhesive properties can be metal compounds which are already approved by the FDA as either food or pharmaceutical additives, such as zinc oxide.

Bioadhesive materials with further enhanced bioadhesive properties can be obtained by incorporating anhydride monomers or oligomers into one of the bioadhesive materials disclosed herein by dissolving, dispersing, or blending, as taught by U.S. Patent Nos. 5,955,096 and 6,156,348, the contents of which are incorporated herein by reference. The anhydride oligomers are formed from organic diacid monomers, preferably the diacids normally found in the Krebs glycolysis cycle. Anhydride oligomers which enhance the bioadhesive properties of a polymer have a molecular weight of about 5000 or less, typically between about 100 and 5000 daltons, or include 20 or fewer diacid units linked by anhydride linkages and terminating in an anhydride linkage with a carboxylic acid monomer.

The oligomer excipients can be blended or incorporated into a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers, including those described above. In one embodiment, anhydride oligomers may be combined with metal oxide particles, such as those described above, to improve bioadhesion even more than with the organic additives alone. Organic dyes, because of their electronic charge and hydrophobicity or hydrophilicity, can either increase or decrease the bioadhesive properties of polymers when incorporated into the polymers.

As used herein, the term "anhydride oligomer" refers to a diacid or polydiacid linked by anhydride bonds, and having carboxy end groups linked to a monoacid such as acetic acid by anhydride bonds. The anhydride oligomers have a molecular weight less than about 5000, typically between about 100 and 5000 daltons, or are defined as including between one to about 20 diacid units linked by anhydride bonds. In one embodiment, the diacids are those normally found in the Krebs glycolysis cycle. The anhydride oligomer compounds have high chemical reactivity.

Control of the rate that an active drug (*e.g.*, a sustained release or controlled delivery

form of a drug) is introduced to a targeted delivery site and its residence time at the targeted delivery site (*e.g.*, site of absorption) is achieved, at least in part, by using excipients, such as polymeric excipients. The exact mechanism by which a polymer interacts with the mucosa or controls the delivery of the drug is at least partially dependent on the rate of polymer hydration and swelling, which is related to its molecular weight. Therefore, any process that significantly reduces the molecular weight of the polymer is likely to affect its ability to control the drug delivery. Oxidative degradation can lead to a loss in molecular weight for several polymers commonly used in controlled release applications (Waterman, K. C., et. al., Pharm. Dev. Technol., 2002, 1-32). In addition to a loss in molecular weight, such degradation in polymers can produce reactive impurities and end groups to compromise the chemical stability of drugs and also their effectiveness as a bioadhesive polymer or release controlling agent. An example of class of controlled release polymers that can degrade to compromise the drug release rate is the polyoxyethylenes, including poly(ethylene oxides) (Polyox™), poly(ethylene glycols), and poly(oxyethylene) alkyl ethers. The polyethylene oxide is usually treated by the manufacturer (Dow chemicals) with 100-1000 ppm of butylated hydroxy toluene (BHT) to reduce such degradation. While this antioxidant is quite effective, it is volatile and can be lost during any heating steps and therefore it is advisable to include an additional antioxidants to the formulation matrix to retain the polymer behavior intact (Waterman, K. C., et. al., Pharm. Dev. Technol., 2002, 1-32).

Hence, it is advisable to incorporate some stabilizers, preferably antioxidants or chelating agents, to inhibit any impurity-related degradation of drugs. Antioxidants can reduce formation of peroxides, but may be less effective in eliminating of peroxides already present in a dosage form. Currently, the marketed form of bupropion hydrochloride is stabilized with an antioxidant like L-cysteine hydrochloride. In contrast, chelating agents such as citric acid, edetic acid, fumaric acid and malic acid are recommended for inhibition of any metal induced oxidation. Chelating agents are generally more effective when added during a granulation step or by coating particles using fluid bed technology, rather than simply during physical mixing. Suitable antioxidants and chelating agents are disclosed in U.S. Pat. No. 6,423,351, the contents of which are incorporated herein by reference, which discloses prevention of drug oxidation using a ferrous ion source. Other suitable antioxidants include vitamin E, vitamin C, butylated hydroxytoluene, and butylated hydroxyanisole.

The pH to which a polymer is exposed can play a significant role in the stabilization of the polymer to oxidation. It is in general more difficult to remove an electron from a

polymer when it is positively charged. For this reason, stability against oxidation is often greater under low pH conditions, which promote protonation of polymers if protonation is possible. In the converse, higher pH conditions, which deprotonate a polymer, generally make a drug more susceptible to oxidation.

U.S. Pat. Nos. 5,358,970; 5,541,231; 5,731,000 and 5,763,493 to Ruff *et al*, the contents of which are incorporated herein by reference, describe a stabilized bupropion hydrochloride formulation having a stabilizer selected from group consisting of L-cysteine hydrochloride, glycine hydrochloride, malic acid, sodium metabisulfite, citric acid, tartaric acid, L-cystine dihydrochloride, ascorbic acid, and isoascorbic(erythorbic) acid. Such stabilizers are useful herein as antioxidants and/or chelating agents. U.S. Pat. No. 6,652,882 to Odidi et. al describes stabilization of drug by a saturated polyglycolised glyceride like Gelucire™, and such compounds are suitable for use in the present invention.

Other oxidation stabilization strategies for bupropion formulations, which are suitable for use herein, include the addition of inorganic acids like hydrochloric acid, phosphoric acid, nitric acid and sulfuric acid (U.S. Pat. No. 5,968,553, the contents of which are incorporated herein by reference); dicarboxylic acids like oxalic acid, succinic acid, adipic acid, fumaric acid, benzoic acid and phthalic acid (U.S. Pat. Nos. 6,194,002; 6,221,917; 6,242,496; 6,482,987 and 6,652,882, the contents of which are incorporated herein by reference); sulfites like potassium metabisulfite and sodium bisulfite (U.S. Pat. No. 6,238,697, the contents of which are incorporated herein by reference); organic esters like L-ascorbic acid palmitate, tocopherol solution in alcohol, butylated hydroxy anisole, tocopherol or tocopherol , vitamin E succinate, vitamin E 700 acetate, and L-ascorbic acid G palmitate (U.S. Pat. No. 6,312,716, the contents of which are incorporated herein by reference). The use of acidified granules of microcrystalline cellulose (U.S. Pat. No. 6,153,223, the contents of which are incorporated herein by reference); salts of organic bases like creatinine hydrochloride, pyridoxine hydrochloride and thiamine hydrochloride and inorganic acid like potassium phosphate monobasic (U.S. Pat. No. 6,333,332, the contents of which are incorporated herein by reference) is also suitable for the present invention.

Typically, antioxidants used in the present invention are selected from ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, malic acid, propyl gallate, sodium bisulfite, sodium sulfite, sodium metabisulfite, potassium metabisulfite, potassium bisulfite, sodium thiosulfate, sodium formaldehyde sulfoxylate, L-ascorbic acid, D-ascorbic acid, acetylcysteine, cysteine, thioglycerol, thioglycollic acid, thiolactic acid, thiourea,

dithiothreitol, dithioerythreitol, glutathione, nordihydroguaiaretic acid, tocopherol, fumaric acid and succinic acid.

The term "acidification" refers to any method of lowering the pH of the bioadhesive polymers either before or after combination with a compatible pharmaceutical drug. Preferably, acidification employs a pharmaceutically acceptable acid to lower pH. Suitable pharmaceutically acceptable acids are well known in the art and include, by way of example only, hydrochloric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, succinic acid, lactic acid, and the like.

Preferably, an antioxidant or a chelating agent is added to a bioadhesive polymer prior to formulating it with a drug. The antioxidant or chelating agent can be added as a dry material or during wet granulation or following the extrusion or annealing process.

Antioxidants (also sometimes referred to as free radical absorbers) self-sacrificially stabilize materials against free radicals (for example, free radicals generated from photooxidation as a result of exposure to sunlight). The antioxidant and the bioadhesive polymer are preferably maintained in sufficiently close proximity such that a synergistic effect on stability of the polymer is achieved. In that regard, a bioadhesive polymer (*e.g.*, a carbidopa-BMA polymer) can be maintained in sufficiently close proximity to the antioxidant moiety to enhance the stability of the carbidopa-based polymer in an environment in which photo-oxidation can occur. Such close proximity is not typically obtained upon mere physical mixing of antioxidant and UV-absorber.

In order to further protect a drug formulation, an antioxidant can be present in combination with a UV-absorber such as PABA or BHT. These components can be localized such that the UV-absorber is within a single molecule (for example, within a single oligomeric or polymer chain). For example, the antioxidant and the UV-absorber can be localized through covalent bonding by reacting (for example, copolymerizing) at least one monomer including or incorporating the antioxidant with at least one monomer including or incorporating the UV-absorber. Antioxidants and UV-absorbers can also be conjugated to a suitably reactive polymer.

Antioxidants, chelating agents and UV-absorbers should be selected such that they do not react with a drug planned to be delivered with the polymer.

Typically, about 0.1% to about 20% by weight, such as about 0.5% to about 10% or about 1% to about 5%, of antioxidant and/or chelating agent is added to a bioadhesive polymer.

a. Materials that can be Incorporated into the Bioadhesive Materials

There is no specific limitation on the material that can be encapsulated within the bioadhesive materials. Any kind of therapeutic, prophylactic or diagnostic agent, including organic compounds, inorganic compounds, proteins, polysaccharides, nucleic acids, or other materials can be incorporated using standard techniques. Flavorants, nutraceuticals, and dietary supplements are among the materials that can be incorporated in the bioadhesive material. In certain embodiments, L-3,4-dihydroxyphenylalanine ("levodopa" or "L-dopa") is incorporated into the bioadhesive material for delivery to a patient. The bioadhesive material may contain carbidopa. In certain embodiments, levodopa and carbidopa are both incorporated in the bioadhesive material. In a preferred embodiment, the bioadhesive material is a coating on an oral dosage formulation which contains levodopa and carbidopa in separate drug layers.

Examples of useful proteins include hormones such as insulin, growth hormones including somatomedins, transforming growth factors and other growth factors, antigens for oral vaccines, enzymes such as lactase or lipases, and digestive aids such as pancreatin.

Examples of useful drugs include ulcer treatments such as Carafate from Marion Pharmaceuticals, antihypertensives or saluretics such as Metolazone from Searle Pharmaceuticals, carbonic anhydrase inhibitors such as Acetazolamide from Lederle Pharmaceuticals, insulin-like drugs such as glyburide, a blood glucose lowering drug of the sulfonylurea class, hormones such as Android F from Brown Pharmaceuticals and Testred (methyltestosterone) from ICN Pharmaceuticals, and antiparasitics such as mebeandazole (VERMOX™, Jannsen Pharmaceutical). Other drugs for application to the vaginal lining or other mucosal membrane lined orifices such as the rectum include spermacides, yeast or trichomonas treatments and anti-hemorrhoidal treatments.

Drugs may be classified using the Biopharmaceutical Classification System (BCS), which separates pharmaceuticals for oral administration into four classes depending on their aqueous solubility and their permeability through the intestinal cell layer. According to the BCS, drug substances are classified as follows:

Class I - High Permeability, High Solubility

Class II - High Permeability, Low Solubility

Class III - Low Permeability, High Solubility

Class IV - Low Permeability, Low Solubility.

The interest in this classification system stems largely from its application in early

drug development and then in the management of product change through its life-cycle. In the early stages of drug development, knowledge of the class of a particular drug is an important factor influencing the decision to continue or stop its development. Examples of various BCS Class of drugs can be found in the following two articles: Kasim N A *et al.*, Molecular Pharmaceutics 1:85-96, (2004) and Rinaki E. *et al*, Pharm. Res. 20(12):1917-1925 (2003), the contents of which are incorporated herein by reference.

Class II drugs are drugs that are particularly insoluble, or slow to dissolve, but that readily are absorbed from solution by the lining of the stomach and/or the intestine. Hence, prolonged exposure to the lining of the GI tract is required to achieve absorption. Such drugs are found in many therapeutic classes.

Many of the known Class II drugs are hydrophobic, and have historically been difficult to administer. Moreover, because of the hydrophobicity, there tends to be a significant variation in absorption depending on whether the patient is fed or fasted at the time of taking the drug. This in turn can affect the peak level of serum concentration, making calculation of dosage and dosing regimens more complex.

Both Class III and IV drugs are often problematic or unsuitable for sustained release or controlled release. Class **III** and Class IV drugs are characterized by insolubility and poor biomembrane permeability and are commonly delivered parenterally. Traditional approaches to parenteral delivery of poorly soluble drugs include using large volumes of aqueous diluents, solubilizing agents, detergents, non-aqueous solvents, or non-physiological pH solutions. These formulations, however, can increase the systemic toxicity of the drug composition or damage body tissues at the site of administration.

In one embodiment, one or more Class I, II, III, or IV drugs are included in a core of a solid oral dosage formulation, and the core is surrounded on at least its circumference by one or more bioadhesive polymers.

Drugs suitable for use in the invention include caffeine, carbamazepine, fluvastatin, Ketoprofen, Metoprolol, Naproxen, Propranolol, Theophylline, Verapamil, Diltiazem, Gabapentin, Levodopa, Divalproex sodium, itraconazole and its relatives, fluoconazole, terconazole, ketoconazole, and saperconazole, griseofulvin and related compounds such as griseoverdin, some anti malaria drugs (*e.g.* Atovaquone), immune system modulators (*e.g.* cyclosporine), cardiovascular drugs (*e.g.* digoxin and spironolactone), ibuprofen, danazol, albendazole, clofazimine, acyclovir, carbamazepine, proteins, peptides, polysaccharides, nucleic acids, nucleic acid oligomers, viruses, Neomycin B, Captopril, Atenolol, Valproic

Acid, Stavudine, Salbutamol, Acyclovir, Methotrexate, Lamivudine, Ergometrine, Ciprofloxacin, Amiloride, Caspofungin, Clorothiazide, Tobramycin, Cyclosporin, Allopurinol, Acetazolamide, Doxycyclin, Dapsone, Nalidixic Acid, Sulfamethoxazole, Tacrolimus, And Paclitaxel.

Both Class III and IV drugs are often problematic or unsuitable for sustained release or controlled release. Class III and Class IV drugs are characterized by insolubility and poor biomembrane permeability and are commonly delivered parenterally. Traditional approaches to parenteral delivery of poorly soluble drugs include using large volumes of aqueous diluents, solubilizing agents, detergents, non-aqueous solvents, or non-physiological pH solutions. These formulations, however, can increase the systemic toxicity of the drug composition or damage body tissues at the site of administration.

In one embodiment, one or more Class I, II, III, or IV drugs are included in a core of a solid oral dosage formulation, and the core is surrounded on at least its circumference by one or more bioadhesive polymers.

In a preferred method for imaging, a radiopaque material such as barium is coated with a bioadhesive material. Radioactive materials or magnetic materials could be used in place or, or in addition to, the radiopaque materials.

b. Tablets

The bioadhesive polymer may be used as one or more layers in a bioadhesive drug delivery tablet formulation. In the preferred embodiment, the formulation is a rate controlled oral dosage formulation (also referred to herein as "BIOROD") in the form of a tablet. The bioadhesive drug delivery formulation contains a core, a bioadhesive coating, and optionally an enteric or non-enteric coating. The core contains one or more drugs, either alone or with a rate controlling membrane system. The core is enveloped on its circumference by a bioadhesive coating. FIGS. 1-9 of the co-pending PCT application PCT/US2006/024352 (filed on June 23, 2006, titled "Bioadhesive Polymers," entire content, including the figures are incorporated herein by reference) illustrate a bioadhesive rate controlled oral dosage formulation (11), which contains at least a bioadhesive polymer (12) and a core (14).

The overall shape of the device has been designed to be compatible with swallowing. As shown in FIG. 1 of PCT/US2006/024352, the core (14) is longitudinally compressed to form a capsule-shaped tablet, which is surrounded on its circumference by a bioadhesive polymeric cylinder (12).

In one embodiment shown in FIG. 2 of PCT/US2006/024352, the active agent is in

the form of microparticles (16), optionally the microparticles are coated with rate controlling polymers (18). In another embodiment shown in FIG. 3 of PCT/US2006/024352, the core (14) is encapsulated in a bioadhesive polymeric cylinder (12), where the cylinder contains restricted release openings at the top and bottom of the cylinder (20).

In yet another embodiment shown in FIG. 4 of PCT/US2006/024352, the core contains multiple drug layers (22 and 24). Optionally, one or more of the drug layers is a controlled release layer, one or more of the layers are immediate release layers, or one of the layers is a controlled release layer while the other layer is an immediate release layer. The tabl*et al*so contains a third drug layer (26) or a separating layer (26). Optionally, the capsule also contains restricted release openings (not shown in figure).

In another embodiment, the capsule is an osmotic drug delivery system. The entire device is coated with a semipermeable membrane, in the preferred embodiment, the membrane is a rigid semipermeable membrane.

As shown in FIG. 5 of PCT/US2006/024352, an osmotic BIOROD system contains a core (14), a semi-permeable coating (28) and a bioadhesive polymer cylinder (12). The semipermeable membrane is located between the core and the bioadhesive layer. The core contains one or more drugs and osmotic agents which pull water across the semi-permeable membrane. Optionally, the capsule contains one or two restricted release openings (20) at the top and/or bottom of the bioadhesive cylinder. In the preferred embodiment, the osmotic delivery system is a "push-pull" system. Examples of this system are illustrated in FIGS. 6-8 of PCT/US2006/024352. The upper chamber contains the drug and is connected to the outside environment via a small exit hole. The lower chamber contains a swellable polymer and an osmotic attractant and may have no exit hole. Suitable osmotic agents include sugars and glycols. Once the tablet has been swallowed, water is drawn into both the upper and lower chambers. Because the lower chamber has no exit hole it expands, pushing the drug layer into the upper chamber, optionally by pushing a plug or diaphragm layer which is located between the drug layer and the push layer. Thus, the drug in the upper chamber is pushed out from the exit hole. As illustrated in FIG. 6 of PCT/US2006/024352, the core contains one layer with an active agent (30), and a second layer with a swellable polymer and osmotic agents (32). The polymer layer (32) is a "push layer" since it pushes drug out of the device when it swells at controlled rates. The system may contain at least one opening (20), as shown in FIG. 6 of PCT/US2006/024352. Optionally, the active agent (30) is separated from the push layer (32) by an insoluble plug (34) (see FIG. 7 of PCT/US2006/024352). In

yet another embodiment illustrated in FIG. 8 of PCT/US2006/024352, the push-pull osmotic delivery system contains an active agent (30) in the drug layer and a swellable polymer and osmotic attractant (32) in the push layer. The drug layer (30) is surrounded on its circumference by a bioadhesive cylinder (12). The lower end of the push layer (32) is adjacent to an insoluble plug (36).

A two-pulse BIOROD system contains either the same drug in controlled release and immediate release layers in a capsule or two different drugs in either controlled release or immediate release layers in the same capsule. One embodiment of a two-pulse BIOROD system is illustrated in FIG. 9 of PCT/US2006/024352, the BIOROD system contains a plug below and above (36) the lower drug layer (24), while the upper drug layer does not contain a plug above the upper drug layer (22). This allows the drug in the upper layer (22) to be released prior to the release of the drug in the lower layer (24).

In yet another embodiment of the oral dosage formulation, the tablet contains precompressed inserts of an active agent, optionally with excipients, (38) and permeation enhancers, optionally with excipients, embedded in a matrix of bioadhesive polymer (40) (see FIG. 10 of PCT/US2006/024352). Drug is released only at the edge of the tablet and the kinetics of drug release is controlled by geometry of the inserts (38). Zero and first order release profiles are achievable with this tablet design and it is possible to have different release rates for permeation enhancer and drug by changing the configuration of the inserts.

i. Methods of Making Bioadhesive Rate Controlling Oral Dosages

The extruded bioadhesive polymer cylinder is formed of one or more bioadhesive polymers. One of the bioadhesive polymers is a biodegradable or non-biodegradable polymer backbone where all or a portion of the monomers that form the polymer are substituted with a compound that includes an aromatic moiety with two or more hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, and a primary amino moiety. Other bioadhesive polymers include poly(fumaric acid-co-sebacic acid) (pFA:SA), as described in U.S. Patent No. 5,955,096 to Mathiowitz *et al.* (*e.g.*, a 20:80 copolymer of p(FA:SA), for example, SPHEROMER™ I [p(FASA) (1:4)]), FA:SA oligomers and metal oxides, as described in U.S. Patent No. 5,985,312 to Jacob *et al.* (for example, SPHEROMER™ II), and other commercially available bioadhesive polymers, such as Gantrez (Polymethyl vinyl ether/maleic anhydride copolymers), CARBOPOL® (Noveon) (high molecular weight homo- and copolymers of acrylic acid crosslinked with a polyalkenyl polyether). Optionally the bioadhesive layer contains one or more plasticizers, pore-forming

agents, and/or solvents. Suitable plasticizers include dibutyl sebacate, dibutyl adipate, dibutyl fumarate, polyethylene glycol, triethyl citrate, and PLURONIC® F68 (BASF). Suitable pore forming agents include sugars and salts, such as sucrose, lactose, dextrose, mannitol, polyethylene glycol, sodium chloride, calcium chloride, phosphate buffer, tris buffer, and citric acid. Thermoplastic polymers can be added to the bioadhesive layer to modify the moldability and mechanical strength of the bioadhesive polymer cylinder. Suitable thermoplastic polymers include polyesters, such as poly(lactic acid-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), poly(caprolactone) (PCL); methylmethacrylates, such as Eudragit RL100, Eudragit RS100, and Eudragit NE 30D; and modified celluloses, such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), cellulose acetate, and ethyl cellulose. The bioadhesive layer may also include or be coated with one or more anti-adherent or anti-tacky (anti-tacking) agents, such as talc, titanium dioxide, fumed silica, colloidal silicon dioxide, glyceryl monostearate, polymeric electrolytes, condensed silicates, polyphosphates, xylin derivatives, aluminum stearate, aluminum laurate, calcium stearate, zinc stearate, kaolin, cornstarch, DL-Leucine, sodium lauryl sulfate, and magnesium stearate.

1. Method for Production of the Hollow Bioadhesive Cylinder

In the preferred embodiment, the extruded polymer cylinder is prepared via hot-melt extrusion process, where the desired bioadhesive polymer is fed into the extruder as a pellet, flake, or powder, optionally along with one or more plasticizers. The materials are blended as they are propelled continuously along a screw through regions of high temperature and pressure to form the polymer extrudate. The extrudate is pushed from the extruder through a die having the desired shape and dimension to form a cylinder. The cylinder is cooled after extrusion. The dimensions of the cylinder can be varied to accommodate the core. The inner diameter of the cylinder can be configured to conform to the desired circumferential dimension of the preformed, pre-pressed core, which contains the therapeutic agent(s). The thickness of the cylinder is determined in part by the polymer/plasticizer type as well its behavior with respect to the external fluid. The bioadhesive nature of the polymer cylinder may also be controlled by mixing different type of polymers and excipients. Inorganic metal oxides may be added to improve the adherence. Pore formers may also be added to control its porosity. Drugs may also be added into the polymer cylinder either as a plasticizer or pore-forming agent. Adding drug to the bioadhesive layer is commonly used to increase porosity (pore-former). Some drugs are small molecules that act as plasticizers. For example, D-DOPA can behave as a plasticizer for D-DOPA-BMA.

Prior to hot-melt extrusion of the hollow cylinder, the bioadhesive polymer, optionally along with a plasticizer in a range from 0.1 to 50% (w/w), preferably 20% (w/w), is mixed in a planetary mixer. Extrusion is performed using either any standard extruder, such as MP 19 TC25 laboratory scale co-rotating twin screw extruded of APV Baker (Newcastle-under-Lyme, UK) or a Killion extruder (Killian extruder Inc., Cedar Grove, NJ). The extruder is typically equipped with a standard screw profile with two mixing sections, an annual die with metal insert for the production of the cylinder and twin screw powder feeder. Typical extrusion conditions are: a screw speed of 5 rpm, a powder feed rate of 0.14 kg/hr and a temperature profile of 125-115-105-80-65 °C from the powder feeder towards the die. The cylinders (typically with an internal diameter of 7 mm and a wall thickness of 1 mm) are typically cut into 1cm long cylinders.

Hollow bioadhesive cylinders or rings can also be made by compressing the bioadhesive granules on a tabletting machine equipped with core rod tooling (Korsch TRP 700/900-NM). These machines with deep fill cavity can be utilized to compress bioadhesive rings. Pre-compression capability of 40-60 kN, final compression force of 100-200 kN, and ejection force of 60 kN may be suitable for making these bioadhesive rings.

2. Method for Production of the Inner Core System

Inner longitudinally compressed core tablets containing the therapeutic agent, and optionally other components, are compressed onto a single or multilayer tableting machine equipped with deep fill or regular tooling. For example, the therapeutic agent, either alone or in combination with a rate controlling polymer and optionally other excipients, is mixed by stirring, ball milling, roll milling or calendaring, and pressed into a solid having dimensions conforming to an internal compartment defined by the extruded polymer cylinder. One or more layers containing different therapeutic agents can be included as a multilayer tablet. The core may be a pre-fabricated insert with a semi-permeable layer on the outside of the core to form an "osmotic system" which is inserted into the bioadhesive cylinder with orifices aligned along the open ends of the cylinder.

3. Method of Insertion of the Core into the Bioadhesive Cylinder

The core, which is preferably in the form of a longitudinally compressed tablet, is inserted into the cylinder and the core and the cylinder, which forms the outer coating, are fused together to produce a solid oral dosage form. The preformed inner core with a diameter slightly smaller than the inner diameter of the cylinder is either manually or mechanically

inserted into the cylinder and heated to fuse the two units. Alternately, the core insertion into the cylinder may also be done by a positive placement core insertion mechanism on the tableting machine. Initially, the extruded cylinder may be placed into the die of the machine followed by insertion of the compressed core into the internal compartment of the cylinder and the two components compressed to get the finished dosage form. Alternatively, the dosage form is prepared via simultaneous extrusion of the bioadhesive cylinder and expandable inner composition using an extruder capable of such an operation.

4. Other Method to Expose the Coated Core

In certain embodiments, lasers may be used to cut the bioadhesive and/or rate controlling material-coated ends to expose the core. The coating can be cut using the CO_2 laser (*e.g.*, 225 Watt CO_2 laser from Control Microsystem), either in the continuous mode or pulse mode. During the continuous mode, a circular cut is made on the ends of the tablets, while in the pulse mode, a circle of orifices is made on the end of the tablets.

The size of the cut maybe controlled to allow different exposure surfaces, and thus different release rates. For example, the end of the coated tablet may be shaped like a cone, and choosing the position of the cut on the cone may allow different sizes of cut surfaces.

In certain embodiments, capsule banding machine may be used to apply the coatings (*e.g.*, the bioadhesive layers and/or enteric coatings, *etc.*) on the peripheral surface of the longitudinally compressed tablets (LCTs) only. A laboratory model capsule banding machine (such as those from Schaefer Technologies, *etc.*) can be used to position the LCTs, and a band can be applied around their circumference. The band can be applied in one stage or two stage banding operations.

c. Administration of Bioadhesive Materials to Patients

The bioadhesive materials may be administered as dry powders in a suspension or in an ointment to the mucosal membranes, via the nose, mouth, rectum, or vagina. Pharmaceutically acceptable carriers for oral or topical administration are known and determined based on compatibility with the polymeric material. Other carriers include bulking agents such as METAMUCIL™. The bioadhesive material may be in a matrix or form a coating in a drug or diagnostic composition which may be administered to a patient by a variety of methods, including transdermal, oral, nasal, vaginal, rectal, ocular, buccal, periodontal, subcutaneous, intramuscular, intraperitoneal, enteral infusion to various GI sites, and intravitreal administration. The material may be administered via inhalation, optionally to deliver the drug formulation to the deep lung.

The bioadhesive material can be used as an adhesive, such as a dental adhesive, a bone cement or glue, a synthetic skin or a wound dressing, a skin plaster or film. These materials can be applied directly to the site in need of treatment.

In one embodiment, the bioadhesive material is a layer in an oral dosage formulation, such as a tablet, optionally a controlled release oral dosage formulation. A patient swallows the oral dosage formulation.

These bioadhesive materials are especially useful for treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. In ulcerative colitis, inflammation is restricted to the colon, whereas in Crohn's disease, inflammatory lesions are often found throughout the gastrointestinal tract, from the mouth to the rectum. Sulfasalazine is one of the drugs that is used for treatment of the above diseases. Sulfasalazine is cleaved by bacteria within the colon to sulfapyridine, an antibiotic, and to 5-aminosalicylic acid, an anti-inflammatory agent. The 5-aminosalicylic acid is the active drug and is active locally. Direct administration of the degradation product (5-aminosalicylic acid) may be more beneficial. A bioadhesive drug delivery system can improve the therapy by retaining the drug for a prolonged time in the intestinal tract. For Crohn's disease, retention of 5-aminosalicylic acid in the upper intestine is of great importance; since bacteria cleave the sulfasalazin in the colon, the only way to treat inflammations in the upper area of the intestine is by local administration of 5-aminosalicylic acid.

Gastrointestinal Imaging Barium sulphate suspension is the universal contrast medium used for examination of the upper gastrointestinal tract, as described by D. Sutton, Ed., *A Textbook of Radiology and Imaging*, Vol. 2, Churchill Livingstone, London (1980), even though it has undesirable properties, such as unpalatability and a tendency to precipitate out of solution. Several properties are critical: (a) particle size: the rate of sedimentation is proportional to particle size (*i.e.*, the finer the particle, the more stable the suspension; (b) non-ionic medium: charges on the barium sulphate particles influence the rate of aggregation of the particles, aggregation is enhanced in the presence of the gastric contents; and (c) solution pH: suspension stability is best at pH 5.3. However, as the suspension passes through the stomach, it is inevitably acidified and tends to precipitate. The encapsulation of barium sulfate in microspheres of appropriate size provides a good separation of individual contrast elements and may, if the polymer displays bioadhesive properties, help in coating, preferentially, the gastric mucosa in the presence of excessive gastric fluid. With bioadhesiveness targeted to more distal segments of the gastrointestinal tract, it may also

provide a kind of wall imaging not easily obtained otherwise.

The double contrast technique, which utilizes both gas and barium sulphate to enhance the imaging process, especially requires a proper coating of the mucosal surface. Air or carbon dioxide must be introduced to achieve a double contrast. This is typically achieved via a nasogastric tube to provoke a controlled degree of gastric distension. Studies indicate that comparable results may be obtained by the release of individual gas bubbles in a large number of individual adhesive microspheres and that this imaging process may be used to image intestinal segments beyond the stomach.

d. Granular bioadhesive polymer formulations

Granulation is a process whereby granules are formed from a bulk substance with or without excipients to improve the properties of the bulk substance. Polymeric granules are solid, dry agglomerates of powder particles (*e.g.*, bioadhesive polymer particles) sufficiently robust to withstand handling. Granules usually contain one or more polymeric ingredients with or without auxiliary substances. Granules can either be used as granules, or may be further modified, *e.g.*, in the manufacturing process of tablets and films, taking advantage of their compactability, flowability, and limited dust formation. Granules can be enlarged through moist granulation processes such as wet granulation or dry granulation, also known as slugging.

Wet granulation is distinguished from dry granulation in that a granulating liquid, such as water, organic liquids or mixtures thereof, is used in wet granulation to produce granules. The advantages of wet granulation include improvement of the cohesiveness and compactability of powders, increase in density, good distribution, reduction of dust and airborne contamination, and prevention of segregation of components.

Dry granulation is used to form granules without using a liquid solution and entails compacting and densifying the powders. Two major modes for compression dry granulation that are conventionally employed are slugging and roller compaction. Slugging involves dry-blending polymeric excipients and then compressing the resultant powder into a large tablet or slug on a compression machine. Roller compaction entails powder compaction wherein compaction pressure and powder feed speed are controlled in a mechanical compression device.

Wet granulation, the process of adding a liquid binder to powders, is one of the most common ways to granulate. Wet granulation allows powder particles to associate with one another, which association may be strengthened by addition of a binder. Most products that

are manufactured as pharmaceuticals are manufactured using a wet granulation process.

Flow properties of the granules may be evaluated by a number of methods known in the art. One way of characterizing formulation properties of a powdered material is by bulk density measurements. A simple method to provide a description of flow characteristics by bulk density measurement is Carr's Compressibility Index (Carr's Index). Carr's Compressibility Index is a simple test to evaluate flowability by comparing both the initial and final (tapped) bulk volumes and the rate of packing down. A useful empirical guide to flow is given by Carr's compressibility index:

Compressibility Index (%)=100 × [(tapped density-initial density)/tapped density]

It is preferred that the granules of the present invention have a Carr's Compressibility Index less than about 34%; more preferably less than about 31%; even more preferably less than about 28%.

Another measurement of particle flow is the internal angle of friction, which can be measured by shear cell experiments. The primary difference in the flow behavior of liquids and powders is in their internal friction. The lack of internal friction of liquids allows them to form level surfaces at rest, while internal friction in powders allows the formation of heaps or other non-level surfaces. Internal friction of powders is typically characterized using a shear cell, which is a device that places a powder sample under known physical stress conditions and measures its response to those stresses, as disclosed in "*Some Measurements of Friction in Simple Powder Beds*," Heistand and Wilcox (*J. Pharm. Sci.* **57**: 1421, 1968, incorporated herein by reference). The response is reported as an angle of internal friction. This parameter is a characteristic of the powders measured and varies between materials. The lower the value of the angle of internal friction, the better flowing the powder is.

Other techniques used to evaluate the flowability of the granules are measuring the Angle of Repose and Angle of Slide.

Angle of Repose: A standard laboratory glass funnel with smooth surfaces and an orifice whose inner diameter is 9 mm is affixed two inches above a stainless steel platform. While keeping the orifice blocked, 10.0 g of powder is loaded into the funnel. By unblocking the orifice, the powder is allowed to flow onto the platform under the force of gravity and, when necessary, with the use of light tapping. The angle of repose is then determined by measuring the apex angle with a protractor (Starrett, Model C183) and performing the following calculation:

Angle of repose = (180°-apex angle)/2

Angle of Slide: The angle of slide is determined by placing 1 g of powder in a 1-inch square stainless steel frame (0.5 inch high), which is resting on a stainless steel platform. The frame is then removed leaving behind an approximately square shaped heap of powder on the platform. One end of the platform is then incrementally raised until the entire powder sample slides off the platform. The angle of slide is then calculated from the height of lift and the length of the platform:

Angle of slide = $\sin^{-1}$(height of lift/length)

In certain embodiments, the invention provides methods for preparing granules comprising a bioadhesive polymer. In certain embodiments, the method comprises:

i) dissolving a bioadhesive polymer in a solvent to form a solution,

ii) combining a second substance with the solution, and

iii) evaporating solvent from said solution under conditions that result in the formation of granules.

The bioadhesive polymer may be any polymer where the polymer itself is bioadhesive, as well as bioadhesive compositions where a polymer is combined with additional compounds, as described previously, In certain aspects, the bioadhesive polymer is selected from SPHEROMER™ I [p(FASA) (1:4)], II, III and IV.

In certain embodiments of the method, the second substance is added in the form of particles or granules, *e.g.*, with a size in the range of 5-500 microns.

The second substance can be a polymer, such as any hydrophobic or hydrophilic polymer, *e.g.*, such as the various polymers described herein. In certain embodiments, the second polymer is a cellulose, such as methylcellulose (MC), carboxymethylcellulose (CMC), hydroxyethylcellulose (HEC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP), vinylpyrrolidone/vinyl acetate copolymer, polyethylene oxide (PEO), methacrylic acid copolymers, methacrylic ester copolymers, ammonioalkyl methacrylate copolymers, cellulose acetate, cellulose acetate butyrate, and ethyl cellulose. Alternatively or additionally, the second polymer can be a polyanhydride polymer or an acidic polymer, *e.g.*, such as a polymer that stabilizes the bioadhesive polymer against degradation, erosion, or dissolution as discussed above. In certain aspects, the bioadhesive polymer and the second polymer are present in the final granules in a ratio of at least 1:1 w:w. In certain aspects, the ratio of bioadhesive polymer to the second polymer is at least 1:5, at least 1:10, at least 1:50, at least 1:100, or at least 1:200 w:w, preferably in the range of 1:2 and 1:50, most preferably between 1:5 and 1:25 w:w.

In certain embodiments, the second substance comprises an acid, such as a weak organic acid, *e.g.*, succinic or fumaric acid. As discussed above, the presence of such acids can stabilize certain bioadhesive polymers, such as SPHEROMER™ III. In certain embodiments, the second substance comprises particles or granules of the acid coated with a rate controlling polymer, such as Eudragit RL100, Eudragit RS100, Eudragit NE30D, or ethylcellulose, *e.g.*, to modulate the rate at which the acid is released into the bioadhesive polymer.

In certain embodiments, the second substance comprises a metal oxide, such as a metal oxide described above as suitable for stabilizing a bioadhesive polymer, *e.g.*, SPHEROMER™ III.

In certain embodiments, the granules are prepared using a fluidized bed granulation method. The fluid bed granulation method (also known as agglomeration) involves suspending particulates in an air stream and then spraying a liquid from the top down onto the fluidized bed. Particles in the path of the spray become slightly wetted and become tacky. The tacky particles collide with other particles and adhere to them to form a granule. In certain embodiments, particles or granules of the second polymer are suspended in an air stream and then a solution of bioadhesive polymer is sprayed.

In another aspect, the granules are further dried and may optionally be ground and/or milled to reduce particle size. Additionally, the granules can be sifted through a United States standard mesh. In certain embodiments the mesh is a United States standard mesh #20 sieve.

The liquid in which the bioadhesive polymer is dissolved can be purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of a polymeric composition in a ketone, an aqueous solution comprising a pharmaceutically acceptable alcohol or ketone, a hydro-alcoholic mixture, a hydro-alcoholic solution of a polymeric composition, In one aspect, the liquid is an alcohol, such as methanol or ethanol.

In another aspect of the invention, bioadhesive granules are provided. In a particular aspect, the bioadhesive granules comprise from about 2% to about 40% of a bioadhesive polymer and about 60% to about 98% of a second polymer. In another aspect, the bioadhesive granules comprise from about 2% to about 20% of a bioadhesive polymer and about 80% to about 98% of a second polymer. Such granules may optionally include additional components, such as excipients, binders, pore-forming agents, *etc.*

The bioadhesive polymer may be any polymer where the polymer itself is bioadhesive, as well as compositions where a non- or poorly bioadhesive polymer is combined with a compound that imparts bioadhesive properties to the composition as a whole as described previously, In certain aspects, the bioadhesive polymer is selected from SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ II, SPHEROMER™ III, and SPHEROMER™ IV.

The second polymer can be any hydrophobic or hydrophilic polymer described herein. In certain embodiments, the second polymer is a non-bioadhesive polymer and/or a hydrophobic polymer. In certain embodiments, the second polymer is a cellulose, such as methylcellulose (MC), carboxymethylcellulose (CMC), hydroxyethylcellulose (HEC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP), vinylpyrrolidone/vinyl acetate copolymer, polyethylene oxide (PEO), methacrylic acid copolymers, methacrylic ester copolymers, ammonioalkyl methacrylate copolymers, cellulose acetate, cellulose acetate butyrate, and ethyl cellulose.

In a particular aspect, the granules are greater than 250 μm in diameter.

When making hollow bioadhesive cylinder, the bioadhesive granules may be compressed on a tabletting machine equipped with core rod tooling (such as a Korsch TRP 700/900-NM type). These machines with deep fill cavity can be utilized to compress bioadhesive rings. Pre-compression capability of 40-60 kN, final compression force of 100-200 kN, and ejection force of 60 kN may be suitable for making these bioadhesive rings. Other equivalent settings may be used with other machine types.

The bioadhesive polymer may also be used as one or more layers in a subject bioadhesive drug delivery tablet formulation.

Polymer-Metal Complexes

As described above, metal can be used to stabilize certain polymers. In addition, as disclosed in U.S. Patent Nos. 5,985,312, 6,123,965 and 6,368,586 (the contents of which are incorporated herein by reference), polymers, such as those named above, having a metal compound incorporated therein have a further improved ability to adhere to tissue surfaces, such as mucosal membranes.

The metal compound incorporated into the polymer can be, for example, a water-insoluble metal oxide. The incorporation of metal compounds into a wide range of different polymers, even those that are not normally bioadhesive, improves their ability to adhere to

tissue surfaces such as mucosal membranes.

The metal compounds preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and hydroxides, including oxides of calcium, iron, copper and zinc. The metal compounds can be combined with a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers.

Metal compounds which can be incorporated into polymers preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and metal hydroxides, which are capable of becoming combined with a polymer to thereby improve the bioadhesiveness of the polymer. As defined herein, a water-insoluble metal compound is defined as a metal compound with little or no solubility in water, for example, less than about 0.0 to 0.9 mg/ml.

The water-insoluble metal compounds can be derived from a wide variety of metals, including, but not limited to, calcium, iron, copper, zinc, cadmium, zirconium and titanium. The water insoluble metal compound preferably is a metal oxide or hydroxide. Water insoluble metal compounds of multivalent metals are preferred. Representative metal oxides suitable for use in the compositions described herein include cobalt oxide (I) (CoO), cobalt oxide (II)(Co_2O_3), selenium oxide (SeO_2), chromium double oxide (CrO_2), manganese oxide (MnO_2), titanium oxide (TiO_2), lanthanum oxide (La_2O_3), zirconium oxide (ZrO_2), silicon oxide (SiO_2), scandium oxide (Sc_2O_3), beryllium oxide (BeO), tantalum oxide (Ta_2O_5), cerium oxide (CeO_2), neodymium oxide (Nd_2O_3), vanadium oxide (V_2O_5), molybdenum oxide (Mo_2O_3), tungsten oxide (WO), tungsten trioxide (WO_3), samarium oxide (Sm_2O_3), europium oxide (Eu_2O_3), gadolinium oxide (Gd_2O_3), terbium oxide (Tb_4O_7), dysprosium oxide (Dy_2O_3), holmium oxide (Ho_2O_3), erbium oxide (Er_2O_3), thulium oxide (Tm_2O_3), ytterbium oxide (Yb_2O_3), lutetium oxide (Lu_2O_3), aluminum oxide (Al_2O_3), indium oxide (InO_3), germanium oxide (GeO_2), antimony oxide (Sb_2O_3), tellurium oxide (TeO_2), nickel oxide (NiO), and zinc oxide (ZnO). Other oxides include barium oxide (BaO), calcium oxide (CaO), nickel oxide (III) (Ni_2O_3), magnesium oxide (MgO), iron oxide (II) (FeO), iron oxide (III) (Fe_2O_3), copper oxide (II) (CuO), cadmium oxide (CdO), and zirconium oxide (ZrO_2).

In certain embodiments, the metal compound is ferric oxide, copper oxide or zinc oxide or a combination thereof. In other embodiments, the metal compound is a zirconate, such as magnesium zirconate or calcium zirconate. In yet other embodiments, the metal compound is a silicate, such as magnesium silicate (*e.g.*, a hydrated magnesium silicate such

as talc) or calcium silicate. Advantageously, metal compounds which are incorporated into polymers are metal compounds which are already approved by the FDA or an equivalent agency as either food or pharmaceutical additives, such as zinc oxide or talc.

Preferred properties defining the metal compound include: (a) substantial insolubility in aqueous environments, such as acidic or basic aqueous environments (such as those present in the gastric lumen); and (b) ionizable surface charge at the pH of the aqueous environment.

The water-insoluble metal compounds can be incorporated into a polymer by, for example, one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; and (d) coating techniques such as fluidized bed, pan coating, or any similar methods known to those skilled in the art, which produce a metal compound enriched layer on the surface of the device. In certain embodiments, nanoparticles or microparticles of the water-insoluble metal compound are incorporated into the polymer, preferably as a uniform dispersion.

In certain embodiments, the metal compound is provided as a fine particulate dispersion of a water-insoluble metal oxide which is incorporated throughout the polymer or at least on the surface of the polymer which is to be adhered to a tissue surface. The metal compound also can be incorporated in an inner layer of the polymer and exposed only after degradation or else dissolution of a "protective" outer layer. For example, a tablet core containing a polymer and metal may be covered with an enteric coating designed to dissolve when exposed to gastric fluid. The metal compound-enriched core then is exposed and become available for binding to GI mucosa.

Fine metal oxide particles can be produced, for example, by micronizing a metal oxide by mortar and pestle treatment to produce particles ranging in size, for example from 10.0 to 300 nm. The metal oxide particles can be incorporated into a polymer, for example, by dissolving or dispersing the particles into a solution or dispersion of the polymer.

Metal compounds are optionally coated with a protective coating, such as an enteric coating or a rate controlling coating. Such coatings are selected in order to release the metal compound only when the system is exposed to gastric fluid or another targeted environment.

Typically, the amount of a metal compound added to a bioadhesive polymer is from about 1% to about 65% by weight, preferably about 5% to about 45% and more preferably about 10% to about 30%.

Advantageously, metal compounds which are incorporated into polymers to improve their bioadhesive properties can be metal compounds which are already approved by the FDA as either food or pharmaceutical additives, such as zinc oxide.

Suitable polymers which can be used and into which the metal compounds can be incorporated include soluble and water-insoluble, and biodegradable and nonbiodegradable polymers, including hydrogels, thermoplastics, and homopolymers, copolymers and blends of natural and synthetic polymers, provided that they have the requisite fracture strength when mixed with a metal compound. In additional to those listed above, representative polymers which can be used in conjunction with a metal compound include hydrophilic polymers, such as those containing carboxylic groups, including polyacrylic acid. Bioerodible polymers including polyanhydrides, poly(hydroxy acids) and polyesters, as well as blends and copolymers thereof also can be used. Representative bioerodible poly(hydroxy acids) and copolymers thereof which can be used include poly(lactic acid), poly(glycolic acid), poly(hydroxy-butyric acid), poly(hydroxyvaleric acid), poly(caprolactone), poly(lactide-co-caprolactone), and poly(lactide-co-glycolide). Polymers containing labile bonds, such as polyanhydrides and polyorthoesters, can be used optionally in a modified form with reduced hydrolytic reactivity. Positively charged hydrogels, such as chitosan, and thermoplastic polymers, such as polystyrene also can be used.

Representative natural polymers which also can be used include proteins, such as zein, modified zein, chitin, chitosan, casein, gelatin, gluten, serum albumin, or collagen, and polysaccharides such as dextrans, polyhyaluronic acid and alginic acid. Representative synthetic polymers include polyphosphazenes, polyamides, polycarbonates, polyacrylamides, polysiloxanes, polyurethanes and copolymers thereof. Celluloses also can be used. As defined herein the term "celluloses" includes naturally occurring and synthetic celluloses, such as alkyl celluloses, cellulose ethers, cellulose esters, hydroxyalkyl celluloses and nitrocelluloses. Exemplary celluloses include ethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate and cellulose sulfate sodium salt.

Polymers of acrylic and methacrylic acids or esters and copolymers thereof can be used. Representative polymers which can be used include poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl

methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

Other polymers which can be used include polyalkylenes such as polyethylene and polypropylene; polyarylalkylenes such as polystyrene; poly(alkylene glycols), such as poly(ethylene glycol); poly(alkylene oxides), such as poly(ethylene oxide); and poly(alkylene terephthalates), such as poly(ethylene terephthalate). Additionally, polyvinyl polymers can be used, which, as defined herein includes polyvinyl alcohols, polyvinyl ethers, polyvinyl esters and polyvinyl halides. Exemplary polyvinyl polymers include poly(vinyl acetate), polyvinyl phenol and polyvinylpyrrolidone.

Water soluble polymers can also be used. Representative examples of suitable water soluble polymers include polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and polyethylene glycol, copolymers of acrylic and methacrylic acid esters, and mixtures thereof. Water insoluble polymers also can be used. Representative examples of suitable water insoluble polymers include ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or -higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethanes, and mixtures thereof. In certain embodiments, a water insoluble polymer and a water soluble polymer are used together, such as in a mixture. Such mixtures are useful in controlled drug release formulations, wherein the release rate can be controlled by varying the ratio of water soluble polymer to water insoluble polymer.

Polymers varying in viscosity as a function of temperature or shear or other physical forces also may be used. Poly(oxyalkylene) polymers and copolymers such as poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO) or poly(ethylene oxide)-poly(butylene oxide) (PEO-PBO) copolymers, and copolymers and blends of these polymers with polymers such as poly(alpha-hydroxy acids), including but not limited to lactic, glycolic and hydroxybutyic acids, polycaprolactones, and polyvalerolactones, can be synthesized or commercially

obtained. For example, polyoxyalkylene copolymers are described in U.S. Patent Nos. 3,829,506, 3,535,307, 3,036,118, 2,979,578, 2,677,700 and 2,675,619. Polyoxyalkylene copolymers are sold, for example, by BASF under the trade name PLURONICS™. These materials are applied as viscous solutions at room temperature or lower which solidify at the higher body temperature. Other materials with this behavior are known in the art, and can be utilized as described herein. These include KLUCEL™ (hydroxypropyl cellulose), and purified konjac glucomannan gum.

Other suitable polymers are polymeric lacquer substances based on acrylates and/or methacrylates, commonly called EUDRAGIT™ polymers (sold by Rohm America, Inc.). Specific EUDRAGIT™ polymers can be selected having various permeability and water solubility, which properties can be pH dependent or pH independent. For example, EUDRAGIT™ RL and EUDRAGIT™ RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, which are present as salts and give rise to the permeability of the lacquer films, whereas EUDRAGIT™ RL is freely permeable and EUDRAGIT™ RS is slightly permeable, independent of pH. In contrast, the permeability of EUDRAGIT™ L is pH dependent. EUDRAGIT™ L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water, but becomes increasingly soluble in a neutral to weakly alkaline solution by forming salts with alkalis. Above pH 5.0, the polymer becomes increasingly permeable.

Polymer solutions that are liquid at an elevated temperature but solid or gelled at body temperature can also be utilized. A variety of thermoreversible polymers are known, including natural gel-forming materials such as agarose, agar, furcellaran, beta-carrageenan, beta-1,3-glucans such as curdlan, gelatin, or polyoxyalkylene containing compounds, as described above. Specific examples include thermosetting biodegradable polymers for *in vivo* use described in U.S. Patent No. 4,938,763, the contents of which are incorporated herein by reference.

Polymer Blends with Monomers and/or Oligomers

Polymers with enhanced bioadhesive properties are provided by incorporating anhydride monomers or oligomers into one of the polymers listed above by dissolving, dispersing, or blending, as taught by U.S. Patent Nos. 5,955,096 and 6,156,348, the contents of which are incorporated herein by reference. The polymers may be used to form drug delivery systems which have improved ability to adhere to tissue surfaces, such as mucosal

membranes. The anhydride oligomers are formed from organic diacid monomers, preferably the diacids normally found in the Krebs glycolysis cycle. Anhydride oligomers which enhance the bioadhesive properties of a polymer have a molecular weight of about 5000 or less, typically between about 100 and 5000 daltons, or include 20 or fewer diacid units linked by anhydride linkages and terminating in an anhydride linkage with a carboxylic acid monomer.

The oligomer excipients can be blended or incorporated into a wide range of hydrophilic and hydrophobic polymers including proteins, polysaccharides and synthetic biocompatible polymers, including those described above. In certain embodiments, anhydride oligomers may be combined with metal oxide particles, such as those described above, to improve bioadhesion even more than with the organic additives alone. Organic dyes, because of their electronic charge and hydrophobicity or hydrophilicity, can either increase or decrease the bioadhesive properties of polymers when incorporated into the polymers.

As used herein, the term "anhydride oligomer" refers to a diacid or polydiacid linked by anhydride bonds, and having carboxy end groups linked to a monoacid such as acetic acid by anhydride bonds. The anhydride oligomers have a molecular weight less than about 5000, typically between about 100 and 5000 daltons, or are defined as including between one to about 20 diacid units linked by anhydride bonds. In certain embodiments, the diacids are those normally found in the Krebs glycolysis cycle. The anhydride oligomer compounds have high chemical reactivity.

The oligomers can be formed in a reflux reaction of the diacid with excess acetic anhydride. The excess acetic anhydride is evaporated under vacuum, and the resulting oligomer, which is a mixture of species which include between about one to twenty diacid units linked by anhydride bonds, is purified by recrystallizing, for example, from toluene or other organic solvents. The oligomer is collected by filtration, and washed, for example, in ethers. The reaction produces anhydride oligomers of mono and poly acids with terminal carboxylic acid groups linked to each other by anhydride linkages.

The anhydride oligomer is hydrolytically labile. As analyzed by gel permeation chromatography, the molecular weight may be, for example, on the order of 200-400 for fumaric acid oligomer (FAPP) and 2000-4000 for sebacic acid oligomer (SAPP). The anhydride bonds can be detected by Fourier transform infrared spectroscopy by the characteristic double peak at 1750 cm^{-1} and 1820 cm^{-1}, with a corresponding disappearance of the carboxylic acid peak normally at 1700 cm^{-1}.

In certain embodiments, the oligomers may be made from diacids described for example in U.S. Patent Nos. 4,757,128, 4,997,904 and 5,175,235, the disclosures of which are incorporated herein by reference. For example, monomers such as sebacic acid, bis(p-carboxy-phenoxy)propane, isophathalic acid, fumaric acid, maleic acid, adipic acid or dodecanedioic acid may be used.

Organic dyes, because of their electronic charge and hydrophilicity or hydrophobicity, may alter the bioadhesive properties of a variety of polymers when incorporated into the polymer matrix or bound to the surface of the polymer. A partial listing of dyes that affect bioadhesive properties include, but are not limited to: acid fuchsin, alcian blue, alizarin red s, auramine o, azure a and b, Bismarck brown y, brilliant cresyl blue ald, brilliant green, carmine, cibacron blue 3GA, congo red, cresyl violet acetate, crystal violet, eosin b, eosin y, erythrosin b, fast green fcf, giemsa, hematoylin, indigo carmine, Janus green b, Jenner's stain, malachite green oxalate, methyl blue, methylene blue, methyl green, methyl violet 2b, neutral red, Nile blue a, orange II, orange G, orcein, paraosaniline chloride, phloxine b, pyronin b and y, reactive blue 4 and 72, reactive brown 10, reactive green 5 and 19, reactive red 120, reactive yellow 2,3, 13 and 86, rose bengal, safranin, Sudan III and IV, Sudan black B and toluidine blue.

Polymers Functionalized with Hydroxy-Substituted Aromatic Groups

Polymers having an aromatic group which contains one or more hydroxyl groups grafted onto them or coupled to individual monomers are also suitable for use in the bioadhesive coatings of the invention. Such polymers can be biodegradable or non-biodegradable polymers. The polymer can be hydrophobic. Preferably, the aromatic group is catechol or a derivative thereof and the polymer contains reactive functional groups. Typically, the polymer is a polyanhydride and the aromatic compound is the catechol derivative DOPA. These materials display bioadhesive properties superior to conventional bioadhesives used in therapeutic and diagnostic applications.

The molecular weight of the suitable polymers and percent substitution of the polymer with the aromatic group may vary greatly. The degree of substitution varies based on the desired adhesive strength, it may be as low as 10%, 25% or 50%, or up to 100% substitution. Generally, at least 50% of the monomers in the polymeric backbone are substituted with at least one aromatic group. Preferably, about 100% of the monomers in the polymeric backbone are substituted with at least one aromatic group. The resulting polymer has a molecular weight ranging from about 1 to 2,000 kDa.

The polymer that forms that backbone of the bioadhesive material can be a biodegradable polymer. Examples of preferred biodegradable polymers include synthetic polymers such as poly hydroxy acids, such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, polyesters, polyurethanes, poly(butyric acid), poly(valeric acid), poly(caprolactone), poly(hydroxybutyrate), poly(lactide-co-glycolide) and poly(lactide-cocaprolactone), and natural polymers such as alginate and other polysaccharides, collagen and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein, modified zein, chitin, chitosan, and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo* and by surface or bulk erosion. The foregoing materials may be used alone, as physical mixtures (blends), or as co-polymers.

Suitable polymers can formed by first coupling the aromatic compound to the monomer and then polymerizing. In this example, the monomers may be polymerized to form a polymer backbone, including biodegradable and non-biodegradable polymers. Suitable polymer backbones include, but are not limited to, polyanhydrides, polyamides, polycarbonates, polyalkylenes, polyalkylene oxides such as polyethylene glycol, polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyethylene, polypropylene, poly(vinyl acetate), poly(vinyl chloride), polystyrene, polyvinyl halides, polyvinylpyrrolidone, polyhydroxy acids, polysiloxanes, polyurethanes and copolymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitrocellulloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulfate sodium salt, and polyacrylates such as poly(methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadccyl acrylate).

A suitable polymer backbone can be a known bioadhesive polymer that is hydrophilic or hydrophobic. Hydrophilic polymers include CARBOPOL™, polycarbophil, cellulose

esters, and dextran.

Non-biodegradable polymers, especially hydrophobic polymers are also suitable as polymer backbones. Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(methacrylic acid), copolymers of maleic anhydride with other unsaturated polymerizable monomers, poly(butadiene maleic anhydride), polyamides, copolymers and mixtures thereof and dextran, cellulose and derivatives thereof.

Hydrophobic polymer backbones include polyanhydrides, poly(ortho)esters, and polyesters such as polycaprolactone. Preferably, the polymer is sufficiently hydrophobic that it is not readily water soluble, for example the polymer should be soluble up to less than about 1% w/w in water, preferably about 0.1% w/w in water at room temperature or body temperature. In the most preferred embodiment, the polymer is a polyanhydride, such as a poly(butadiene maleic anhydride) or another copolymer of maleic anhydride. Polyanhydrides may be formed from dicarboxylic acids as described in U.S. Patent No. 4,757,128 to Domb *et al.*, incorporated herein by reference. Suitable diacids include aliphatic dicarboxylic acids, aromatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acid, combinations of aromatic, aliphatic and aromatic-aliphatic dicarboxylic acids, aromatic and aliphatic heterocyclic dicarboxylic acids, and aromatic and aliphatic heterocyclic dicarboxylic acids in combination with aliphatic dicarboxylic acids, aromatic-aliphatic dicarboxylic acids, and aromatic dicarboxylic acids of more than one phenyl group. Suitable monomers include sebacic acid (SA), fumaric acid (FA), bis(p-carboxyphenoxy)propane (UP), isophthalic acid (IPh), and dodecanedioic acid (DD).

A wide range of molecular weights are suitable for the polymer that forms the backbone of the bioadhesive material. The molecular weight may be as low as about 200 Da (for oligomers) up to about 2,000 kDa. Preferably the polymer has a molecular weight of at least 1,000 Da, more preferably at least 2,000 Da, most preferably the polymer has a molecular weight of up to 20 kDa or up to 200 kDa. The molecular weight of the polymer may be up to 2,000 kDa.

The range of substitution on the polymer varies greatly and depends on the polymer used and the desired bioadhesive strength. For example, a butadiene maleic anhydride copolymer that is 100% substituted with DOPA will have the same number of DOPA molecules per chain length as a 67% substituted ethylene maleic anhydride copolymer. Typically, the polymer has a percentage substitution ranging from 10% to 100%, preferably ranging from 50% to 100%.

The polymers and copolymers that form the backbone of the bioadhesive material include reactive functional groups that interact with the functional groups on the aromatic compound.

It is desirable that the polymer or monomer that forms the polymeric backbone contains accessible functional groups that easily react with molecules contained in the aromatic compounds, such as amines and thiols. In a preferred embodiment, the polymer contains amino reactive moieties, such as aldehydes, ketones, carboxylic acid derivatives, cyclic anhydrides, alkyl halides, aryl azides, isocyanates, isothiocyanates, succinimidyl esters or a combination thereof.

Preferably, the aromatic compound containing one or more hydroxyl groups is catechol or a derivative thereof. Optionally, the aromatic compound is a polyhydroxy aromatic compound, such as a trihydroxy aromatic compound (*e.g.,* phloroglucinol) or a multihydroxy aromatic compound (*e.g.,* tannin). The catechol derivative may contain a reactive group, such as an amino, thiol, or halide group. The preferred catechol derivative is 3,4-dihydroxyphenylalanine (DOPA), which contains a primary amine. Tyrosine, the immediate precursor of DOPA, which differs only by the absence of one hydroxyl group in the aromatic ring, can also be used. Tyrosine is capable of conversion (*e.g.,* by hydroxylation) to the DOPA form. A particularly preferred aromatic compound is an amine-containing aromatic compound, such as an amine-containing catechol derivative (*e.g.*, dopamine).

Two general methods are used to form the polymer product. In one example, a compound containing an aromatic group which contains one or more hydroxyl groups is grafted onto a polymer. In this example, the polymeric backbone is a biodegradable polymer. In a second example, the aromatic compound is coupled to individual monomers and then polymerized.

Any chemistry which allows for the conjugation of a polymer or monomer to an aromatic compound containing one or more hydroxyl groups can be used, for example, if the aromatic compound contains an amino group and the monomer or polymer contains an amino reactive group, this modification to the polymer or monomer is performed through a nucleophilic addition or a nucleophilic substitution reaction, such as a Michael-type addition reaction, between the amino group in the aromatic compound and the polymer or monomer. Additionally, other procedures can be used in the coupling reaction. For example, carbodiimide and mixed anhydride based procedures form stable amide bonds between carboxylic acids or phosphates and amino groups, bifunctional aldehydes react with primary

amino groups, bifunctional active esters react with primary amino groups, and divinylsulfone facilitates reactions with amino, thiol, or hydroxy groups.

The aromatic compounds are grafted onto the polymer using standard techniques to form the bioadhesive material. In one example, L-DOPA is grafted to maleic anhydride copolymers by reacting the free amine in L-DOPA with the maleic anhydride bond in the copolymer.

A variety of different polymers can be used as the backbone of the bioadhesive material, as described above. Additional representative polymers include 1:1 random copolymers of maleic anhydride with ethylene, vinyl acetate, styrene, or butadiene. In addition, a number of other compounds containing aromatic rings with hydroxy substituents, such as tyrosine or derivatives of catechol, can be used in this reaction.

In another embodiment, the polymers are prepared by conjugate addition of a compound containing an aromatic group that is attached to an amine to one or more monomers containing an amino reactive group. In a preferred method, the monomer is an acrylate or the polymer is acrylate. For example, the monomer can be a diacrylate such as 1,4-butanediol diacrylate, 1,3-propanediol diacrylate, 1,2-ethanediol diacrylate, 1,6-hexanediol diacrylate, 2,5-hexanediol diacrylate or 1,3-propanediol diacrylate. In an example of the coupling reaction, the monomer and the compound containing an aromatic group are each dissolved in an organic solvent (*e.g.*, THF, CH_2Cl_2, methanol, ethanol, $CHCl_3$, hexanes, toluene, benzene, CCl_4, glyme, diethyl ether, *etc.*) to form two solutions. The resulting solutions are combined, and the reaction mixture is heated to yield the desired polymer. The molecular weight of the synthesized polymer can be controlled by the reaction conditions (*e.g.*, temperature, starting materials, concentration, solvent, *etc.*) used in the synthesis.

For example, a monomer, such as 1,4-phenylene diacrylate or 1,4-butanediol diacrylate having a concentration of 1.6 M, and DOPA or another primary amine containing aromatic molecule are each dissolved in an aprotic solvent such as DMF or DMSO to form two solutions. The solutions are mixed to obtain a 1:1 molar ratio between the diacrylate and the amine group and heated to 56 °C to form a bioadhesive material.

<u>*Bioadhesive Polymer Blends*</u>

Hydrophobic polymers, such as polyesters, poly (anhydrides), ethyl cellulose, even if possibly non-adhesive on their own, may nevertheless be made bioadhesive simply by physically mixing the hydrophobic polymers with one or more suitable compounds (such as catechols or derivatives L-DOPA, D-DOPA, dopamine, or carbidopa, *etc.*) to create

"bioadhesive compositions." Similarly, metal oxides may also be used for this purpose.

The molecular weight of the bioadhesive polymers and percent substitution of the polymers with residues of the compounds disclosed may vary greatly. The degree of substitution varies based on the desired adhesive strength, it may be as low as 10%, 20%, 25%, 50%, or up to 100% substitution. On average, at least 50% of the repeat units in the polymeric backbone are substituted with at least one residue. In one particular embodiment, 75-95% of the residues in the backbone are substituted with at least one residue. In another particular embodiment, on average 100% of the repeat units in the polymeric backbone are substituted with at least one residue. The resulting bioadhesive polymer typically has a molecular weight ranging from about 1 to 2,000 kDa, such as 1 to 1,000 kDa, 10 to 1,000 kDa or 100 to 1,000 kDa. Polymers used in bioadhesive compositions typically have the same range of molecular weights.

Unlike the bioadhesive polymers described above, there is typically no covalent bond formed between the compounds and the polymer in the bioadhesive compositions (*i.e.*, the polymer does not chemically react with the compound, although hydrogen bonds, ionic bonds and/or van der Waals interactions can occur).

Suitable polymers for use in bioadhesive compositions are described above. Typically, the polymer itself may not be bioadhesive, but the polymer can be bioadhesive (*e.g.*, a polymer with hydrogen bond-forming pendant groups). Preferably, the polymer is a hydrophobic polymer such as a poly(lactone), *e.g.*, poly(caprolactone).

To form the bioadhesive compositions of the invention, typically a polymer and a suitable compound are dissolved in a compatible solvent and mixed together. The solvent is then evaporated, preferably at a controlled temperature and rate of removal. Alternatively or in combination with general evaporation, the bioadhesive composition can be spray dried or dried at room temperature.

In another example, a mixture of a polymer and a suitable compound are melted at or slightly above the melting point of the polymer, typically while being mixed. Both the polymer and the suitable compound should be selected such that they are chemically stable (*e.g.*, do not decompose, do not become oxidized) at the melting point temperature. After the composition has re-solidified, it can be milled in order to obtain particles of the desired size.

The subject bioadhesive compositions can also be prepared by dry mixing of a polymer and a suitable compound, provided that the suitable compound is sufficiently distributed throughout the composition.

In each of the above methods, additional components can be added to the mixture prior to dissolution, melting and/or mixing. The additional components are preferably stable under the conditions the mixture is exposed to. In particular, active agents should be stable at the melting point temperature if that method is employed.

The weight ratio of polymer to the suitable compound in a bioadhesive composition can be selected to give the desired amount of bioadhesion. Typically, the weight ratio of polymer to compound is 9:1 to 1:9, such as 3:1 to 1:3 or 2:1 to 1:2. For example, when the polymer is predominant component, the weight ratio is 9:1 to 1:1, 3:1 to 1:1 or 2:1 to 1:1.

In the subject methods and pharmaceutical compositions, the suitable compounds (such as L-DOPA, D-DOPA, dopamine, or carbidopa, *etc.*) may be used as agents to render the hydrophobic polymers bioadhesive, and/or be used as active ingredients in the pharmaceutical composition to be delivered to the patient. Thus, in certain embodiments, if carbidopa is used as part of the bioadhesive layer (for example, as the bioadhesive material on the shell of Figure 5, or as the layer to coat the core comprising the second zero-order release portion), the total carbidopa dosage may be adjusted to account for the release of carbidopa from the bioadhesive material.

Similarly, in certain embodiments, when L- or D-dopa is used as the suitable compound to render the hydrophobic polymer bioadhesive, the dosage of total levodopa or precursor thereof may be adjusted elsewhere in, for example, the relevant portion or sub-portions of the IR or CR (controlled release, *e.g.*, zero-order release rate portion).

In certain embodiments, a higher proportion of L-dopa (or D-Dopa) may be used to achieve a significant amount of release (*e.g.*, more or less immediate release) from the polymers. In other embodiments, less L- or D-Dopa may be used such that the polymer is still adhesive, but the release of L- or D-Dopa from the bioadhesive polymer is less significant compared to the levodopa or precursors thereof in IR, and/or one or more other portions or sub-portions of the subject dosage form.

Coatings

Preferred bioadhesive coatings do not appreciably swell upon hydration, such that they do not substantially inhibit or block movement (*e.g.*, of ingested food) through the gastrointestinal tract, as compared to the polymers disclosed by Duchene *et al.* Generally, polymers that do not appreciably swell upon hydration include one or more hydrophobic regions, such as a polymethylene region (*e.g.*, $(CH_2)_n$, where n is 4 or greater). The swelling of a polymer can be assessed by measuring the change in volume when the polymer is

exposed to an aqueous solution. Polymers that do not appreciably swell upon hydration expand in volume by 50% or less when fully hydrated. Preferably, such polymers expand in volume by less than 25%, less than 20%, less than 15%, less than 10% or less than 5%. Even more preferably, the bioadhesive coatings are mucophilic. A polymer that does not appreciably swell upon hydration can be mixed with a polymer that does swell (*e.g.*, Carbopol™, poly(acrylic acid), provided that the amount of swelling in the polymer does not substantially interfere with bioadhesiveness.

In certain embodiments, the bioadhesive polymeric coating has two layers, an inner bioadhesive layer that does not substantially swell upon hydration and an outer bioadhesive layer that is readily hydratable and optionally bioerodable, such as one comprised of Carbopol™.

The bioadhesive polymers discussed above can be mixed with one or more plasticizers or thermoplastic polymers. Such agents typically increase the strength and/or reduce the brittleness of polymeric coatings. Examples of plasticizers include dibutyl sebacate, polyethylene glycol, triethyl citrate, dibutyl adipate, dibutyl fumarate, diethyl phthalate, ethylene oxide-propylene oxide block copolymers such as Pluronic™ F68 and di(sec-butyl) fumarate. Example of thermoplastic polymers include polyesters, poly(caprolactone), polylactide, poly(lactide-co- glycolide), methyl methacrylate (*e.g.*, EUDRAGIT™), cellulose and derivatives thereof such as ethyl cellulose, cellulose acetate and hydroxypropyl methyl cellulose (HPMC) and large molecular weight polyanhydrides. The plasticizers and/or thermoplastic polymers are mixed with a bioadhesive polymer to achieve the desired properties. Typically, the proportion of plasticizers and thermoplastic polymers, when present, is from 0.5% to 40% by weight.

In certain embodiments, the bioadhesive polymer coating, in a dry packaged form of a tablet, is a hardened shell.

A tablet or a drug eluting device can have one or more coatings in addition to the bioadhesive polymeric coating. These coatings and their thickness can, for example, be used to control where in the gastrointestinal tract the bioadhesive coating becomes exposed. In one example, the additional coating prevents the bioadhesive coating from contacting the mouth or esophagus. In another example, the additional coating remains intact until reaching the small intestine (*e.g.*, an enteric coating).

Examples of coatings include methylmethacrylates, zein, modified zein, chitin, chitosan, cellulose acetate, cellulose phthalate, HMPC, sugars, enteric polymers, gelatin and

shellac. Premature dissolution of a tablet in the mouth can be prevented with hydrophilic polymers such as HPMC or gelatin.

Coatings used in tablets of the invention typically include a pore former, such that the coating is permeable to the drug. Exemplary pore formers include: sugar, mannitol, HPC (hydroxypropyl cellulose), HPMC, dendrites, NaCl, *etc.*

Tablets and drug eluting devices of the invention can be coated by a wide variety of methods. Suitable methods include compression coating, coating in a fluidized bed or a pan, enrobing, and hot melt (extrusion) coating, *etc.* Such methods are well known to those skilled in the art.

All the above compositions, derivatives, precursors, additional components that can be used with levodopa / carbidopa, dosage forms, methods of making and using, *etc.*, are adaptable or directly useable with the instant invention, and are thus expressly incorporated herein by reference.

Examples:

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

Example 1 ***In vivo Release of Levodopa and Carbidopa***

The following experiment was designed to determine if effective levodopa concentration *in vivo* is increased at the presence of a higher ratio of carbidopa to levodopa (as compared to that used in conventional therapy).

SINEMET® CR tablets (50 mg carbidopa / 200 mg levodopa) were administered to fed beagle dogs either alone or after pre-dosing with 12.5 mg and 25 mg of carbidopa, and plasma concentrations of carbidopa and levodopa were measured over time (data not shown). The $AUC_{0\text{-}24}$ (Area Under the Concentration-time curve for 24 hours) for each set of measurements were also summarized in Table 1 below.

Table 1 AUC_{0-24} (ng/mL × hr) of Carbidopa and Levodopa

Drug	SINEMET® CR	Carbidopa 12.5 mg + SINEMET® CR	Carbidopa 25 mg + SINEMET® CR
Levodopa	3903 ± 298	8640 ± 2064	6998 ± 3834
Carbidopa	215 ± 43	592 ± 303	956 ± 534

Table 1 clearly shows a significant (almost 100%) increase in both peak concentrations for carbidopa and levodopa, and AUC_{0-24}, despite the fact that the total amount of levodopa in all experiments remained the same (*e.g.*, 200 mg). This demonstrates that higher ratio of carbidopa / levodopa in the immediate release portion, or pre-dosing using carbidopa can lead to a higher effective levodopa concentration or AUC_{0-24} in animal models.

Example 2 ***In vivo Pharmacokinetic Performance of SINEMET® CR 50-200 Tablets in Fed Beagle Dogs and Healthy Young Human Volunteers, Lot # N4682***

The *in vivo* performance of SINEMET® CR 50-200 tablets was evaluated in beagle dogs. SINEMET® CR tablets were administered to cohorts of six beagle dogs in the fed state and plasma levels of levodopa and carbidopa were measured using HPLC analysis. Figure 43 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC_{0-24}), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 2a.

In addition, the *in vivo* performance of SINEMET® CR 50-200 tablets was evaluated in healthy human volunteers. The tablets were administered to twelve healthy volunteers after having a light breakfast (1600 kJ). Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 54 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC_{0-24}), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 2b.

Table 2a. Pharmacokinetic Data for SINEMET® CR 50-200 Tablets, Lot # N4682, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC_{0-24}), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max}).

Formulation	AUC_{0-24} (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
SINEMET® CR 50-200 Tablets	3,903	1,663	2

Table 2b. Pharmacokinetic Data for SINEMET® CR 50-200 Tablets, Lot # N4682, in Fed Healthy Human Volunteers; the area under the plasma levodopa vs. time curve (AUC_{0-24}), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max}).

Fasting Period	AUC_{0-24} (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
Fed	3,249 ± 1,830	897 ± 524	3.7 ± 1.1

Example 3 *In vitro* Dissolution and *In vivo* Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Multilayer Extended Release Tablets, Lot # 603-243

The *in vitro* dissolution profile of bioadhesive levodopa-carbidopa multilayer extended release tablets, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolu-tion profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 44.

The *in vivo* performance of bioadhesive levodopa-carbidopa multilayer extended release tablets was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed and fasted states. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figures 45 and 46 show the plasma concentration profiles of levodopa and carbidopa in the fed and fasted states, respectively. The pharmacokinetic data including the area under the plasma levodopa vs. time curve

($AUC_{0\text{-}24}$), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 3a.

Table 3a. Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Multilayer Extended Release Tablets, Lot # 603-243, in Fed and Fasted Beagle Dogs; the area under the plasma levodopa vs. time curve ($AUC_{0\text{-}24}$), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max}).

Fasting Period	**$AUC_{0\text{-}24}$ (ng/ml.hr)**	**C_{max} (ng/ml)**	**T_{max} (hr)**
Fed	15,927	2,326	4.5
Fasted	7,175	3,073	0.9

The *in vivo* performance of bioadhesive levodopa-carbidopa multilayer extended release tablets was evaluated in healthy human volunteers. The tablets were administered to six healthy volunteers after having a light breakfast (1600 kJ). Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 55 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve ($AUC_{0\text{-}24}$), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 3b.

Table 3b. Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Multilayer Extended Release Tablets, Lot # 603-243, in Fed Healthy Human Volunteers; the area under the plasma levodopa vs. time curve ($AUC_{0\text{-}24}$), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max}).

Fasting Period	**$AUC_{0\text{-}24}$ (ng/ml.hr)**	**C_{max} (ng/ml)**	**T_{max} (hr)**
Fed	3,074 ± 789	556 ± 110	3.9 ± 2.7

Example 4 ***In vitro Dissolution and in vivo Pharmacokinetic Performance of SINEMET® CR 50-200 Tablets, containing 50 mg Carbidopa and 200 mg Levodopa, Lot # N4682***

The *in vitro* dissolution profile of SINEMET® CR 50-200 tablets, containing 50 mg

carbidopa and 200 mg levodopa were obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1N HCl - pH 1.2 solution, in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolution profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 49.

The *in vivo* pharmacokinetic performance of SINEMET® CR 50-200 tablets was evaluated in beagle dogs. SINEMET® CR tablets were administered to cohorts of six beagle dogs in the fed state and plasma levels of levodopa and carbidopa were measured using HPLC analysis. Figures 47 and 48 show the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC_{0-24}), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are in Table 4.

Table 4. Pharmacokinetic Data for SINEMET® CR 50-200 Tablets, Lot # N4682, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC_{0-24}), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Formulation	**AUC_{0-24} (ng/ml.hr)**	**C_{max} (ng/ml)**	**T_{max} (hr)**
SINEMET® CR 50-200 Tablets	3,903	1,663	2

An exemplary carbidopa extended release formulation is a trilayer tablet system, containing about 100 mg carbidopa anhydrous. In general, the system consists of three matrix layers: two inactive outer layers composed of a bioadhesive polymer composition and a middle active layer composed of a controlled-release (CR) carbidopa formulation. The three layers may be pressed together into a capsule shaped tablet, such as those sizing roughly 0.3" × 0.9". In the stomach, the bioadhesive layers hydrate in the presence of gastric fluids. The tablet then reversibly attaches to the gastric mucosa and resides in the stomach over an extended duration. While adhered to the stomach wall, the controlled-release layer hydrates in the presence of gastric fluid and uniformly dissolves/erodes from the open edges of the tablet, releasing carbidopa into the gastric contents in a regulated manner, such as within 10 to 12 hours. Subsequent to complete or nearly complete dissolution of the active layer composition, the tablet splits in two halves, mainly comprising insoluble bioadhesive layers. Any residual

amounts of the active layer composition on bioadhesive layers are dissolved in stomach or during the transition of bioadhesive layers through the small intestine. The bioadhesive layers are finally excreted in the feces.

The following examples describe material compositions and methods of manufacture of carbidopa extended release formulations. In particular, examples of carbidopa trilayer extended release tablet formulation.

Example 5 ***Low-shear Granulation of Carbidopa***

Carbidopa granules are produced with a low-shear granulation method comprising:

(1) Weighing carbidopa, optionally a bioadhesive polymer composition such as SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant in a cylindrical container, using, *e.g.*, an end-over-end ATR rotator, such as model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer (Hobart Corporation, Troy, OH) operating at the speed setting #1, for about 5-15 min, forming a uniform dry mix.

(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluids are mainly selected from purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone. The granulation is conducted in a 500-mL cylindrical vessel with manual mixing, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, depending on the batch size.

(4) Drying the wet granulation from step (3) in a Precision gravity oven, operating at 50 °C, for about 4-24 hrs. Alternatively, the granulation is dried in a fluidized bed drier, *e.g.*, Vector MFL.01 Micro Batch Fluid Bed System (Vector Corporation, Marion, IA) operating at an inlet air flow rate of about 100-300 lpm (liters per minute) and an inlet air temperature of about 50 °C, for about 1-3 hrs.

(5) Grinding the dried granulation from step (4), *e.g.*, by using a pestle in a mortar, followed by sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Blending the sieved granulation from step (5) with a lubricant in a cylindrical container, *e.g.*, using an end-over-end ATR rotator, such as model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer, operating at the speed setting #1, or in Maxiblend V-shell blender (GlobePharma, New Brunswick, NJ) with a 0.5-, 1-, or 2-qt V-shell, for 5-15 min., forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 6 ***High-shear Granulation of Carbidopa –p***

Carbidopa granules are produced with high-shear granulation method comprising:

(1) Weighing carbidopa, optionally a bioadhesive polymer composition such as SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant in a 2- or 4-liter product bowl, such as the Pharmx High Shear Granulator and Mixer type (Fluid Air Inc., Aurora, IL) at a mixing speed of about 100-200 rpm for 3-5 min, forming a uniform dry mix.

(3) Granulating the dry mix from step (2) under high shear with a granulation fluid, forming a wet granulation. The granulation fluids are mainly selected from purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone. The granulation is conducted, *e.g.*, at impeller speed of 100-150 rpm and chopper speed of 1000-2000 rpm.

(4) Drying the wet granulation from step (3), *e.g.*, in a Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of about 100-300 lpm (liters per minute) and an inlet air temperature of about 50 °C, for about 1-3 hrs. Alternatively,

the wet granulation is dried, *e.g.*, in a Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL).

(5) Milling and sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Blending the sieved granulation from step (5) with a lubricant, *e.g.*, in Maxiblend V-shell blender with a 0.5-, 1-, or 2-qt V-shell, for 5-15 min., forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 7 ***Low-shear Granulation of a Bioadhesive Polymer, SPHEROMER™ I [p(FASA) (1:4)] or SPHEROMER™ III --p***

Bioadhesive Polymer, SPHEROMER™ I [p(FASA)] or SPHEROMER™ III granules are produced with a low-shear granulation method comprising:

(1) Weighing the bioadhesive polymer, optionally a hydrophobic polymer composition, optionally a hydrophilic polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant in a cylindrical container, *e.g.*, using an end-over-end ATR rotator, such as model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for about 5-15 min, forming a uniform dry mix.

(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluids are mainly selected from a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone. The granulation is conducted in a small cylindrical vessel with manual mixing, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, depending on the batch size.

(4) Drying the wet granulation from step (3) in a Precision gravity oven, operating at about 50 °C, for about 8-24 hrs. Alternatively, the granulation is dried in a fluidized bed drier, *e.g.*, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of about 100-300 lpm (liters per minute) and an inlet air temperature of

about 55 °C. Still alternatively, the wet granulation is dried in a system of the type Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL).

(5) Grinding the dried granulation from step (4), *e.g.*, by using a pestle in a mortar, followed by sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Optionally blending the sieved granulation from step (5) with a lubricant in a cylindrical container, *e.g.*, using an end-over-end ATR rotator, such as model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer, operating at the speed setting #1, for about 5-15 min, forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 8 ***High-shear Granulation of a Bioadhesive Polymer, SPHEROMER™ I [p(FASA) (1:4)] or SPHEROMER™ III –p***

SPHEROMER™ granules are produced with a high-shear granulation method comprising:

(1) Weighing SPHEROMER™, optionally a hydrophobic polymer composition, optionally a hydrophilic polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, in a 2- or 4-liter product bowl of the type of Pharmx High Shear Granulator and Mixer (Fluid Air Inc., Aurora, IL), at a mixing speed of about 100-200 rpm for about 3-5 min., forming a uniform dry mix.

(3) Granulating the dry mix from step (2) under high shear with a granulation fluid, forming a wet granulation. The granulation fluids are mainly selected from purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone. The granulation is conducted at impeller speed of about 20-200 rpm and chopper speed of about 1000-4000 rpm.

(4) Drying the wet granulation from step (3), *e.g.*, in a Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of about 100-300 lpm (liters per

minute) and an inlet air temperature of about 50 °C, for about 1-3 hrs. Alternatively, the wet granulation is dried in a system of the type Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL).

(5) Milling and sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Optionally blending the sieved granulation from step (5) with a lubricant, *e.g.*, in Maxiblend V-shell blender with a 0.5-, 1-, or 2-qt V-shell, for about 5-15 min., forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 9 ***Low-shear Granulation of a Non-Bioadhesive Hydrophobic Polymer***

Non-bioadhesive hydrophobic polymer granules are produced with a low-shear granulation method comprising:

(1) Weighing a non-bioadhesive hydrophobic polymer, optionally a hydrophilic polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant in a cylindrical container, *e.g.*, using an end-over-end ATR rotator, such as model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for about 5-15 min., forming a uniform dry mix.

(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluids are mainly selected from a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone. The granulation is conducted in a small cylindrical vessel with manual mixing, or in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, depending on the batch size.

(4) Drying the wet granulation from step (3) in a Precision gravity oven, operating at about 50 °C, for about 8-24 hrs. Alternatively, the granulation is dried in a fluidized bed drier, of the type of Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of about 100-300 lpm (liters per minute) and an inlet air

temperature of about 55 °C. Still alternatively, the wet granulation is dried in a system of the type Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL).

(5) Grinding the dried granulation from step (4), *e.g.*, by using a pestle in a mortar, followed by sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Optionally blending the sieved granulation from step (5) with a lubricant in a cylindrical container, *e.g.*, using an end-over-end ATR rotator, such as model RKVS, or in a planetary type mixer, *e.g.*, Hobart Mixer, operating at the speed setting #1, for about 5-15 min., forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 10 ***High-shear Granulation of a Non-Bioadhesive Hydrophobic Polymer***

Non-bioadhesive hydrophobic polymer granules are produced with a high-shear granulation method comprising:

(1) Weighing a non-bioadhesive hydrophobic polymer, optionally a hydrophilic polymer composition, and pharmaceutically acceptable excipients.

(2) Blending the weighed ingredients from step (1) excluding a lubricant, *e.g.*, in a 2- or 4-liter product bowl of the type Pharmx High Shear Granulator and Mixer (Fluid Air Inc., Aurora, IL), at a mixing speed of about 100-200 rpm for about 3-5 min., forming a uniform dry mix.

(3) Granulating the dry mix from step (2) under high shear with a granulation fluid, forming a wet granulation. The granulation fluids are mainly selected from purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone. The granulation is conducted at impeller speed of about 20-200 rpm and chopper speed of about 1000-4000 rpm.

(4) Drying the wet granulation from step (3) in a system of the type Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of about 100-300

lpm (liters per minute) and an inlet air temperature of about 50 °C, for about 1-3 hrs. Alternatively, the wet granulation is dried in a system of the type Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL).

(5) Milling and sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Optionally blending the sieved granulation from step (5) with a lubricant, *e.g.*, in Maxiblend V-shell blender with a 0.5-, 1-, or 2-qt V-shell, for about 5-15 min., forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 11 ***Fluidized Bed Granulation of a non-Bioadhesive Hydrophobic Polymer with Bioadhesive SPHEROMER™ III***

Granules are produced with a fluidized bed granulation method comprising:

(1) Weighing a non-bioadhesive hydrophobic polymer, optionally a hydrophilic polymer composition, and pharmaceutically acceptable excipients.

(2) Transferring the weighed ingredients from step (1) excluding a lubricant to the product bowl of a system of the type Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL), and pre-heating by fluidization at an inlet air temperature of about 30-40 °C and flow rate of about 15-25 scfm (standard cubic feet per minute) for about 2-5 min.

(3) Granulating the pre-heated material mix from step (2) under fluidization with a granulation fluid in a top-spray mode. The granulation fluid is mainly an alcoholic solution of a SPHEROMER™ III composition. The granulation is conducted at an inlet air temperature of about 30-40 °C and flow rate of about 15-25 scfm.

(4) Drying the granulation from step (3) under fluidization at an inlet air temperature of about 30-35 °C and flow rate of about 15-25 scfm.

(5) Milling and sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Optionally, blending the sieved granulation from step (5) with a lubricant, *e.g.*, in Maxiblend V-shell blender with a 0.5-, 1-, or 2-qt V-shell, for about 5-15 min., forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 12 ***Fluidized Bed Granulation of a non-Bioadhesive Hydrophobic Polymer with a Hydrophilic or Hydrophobic Polymer***

Granules are produced with a fluidized bed granulation method comprising:

(1) Weighing a non-bioadhesive hydrophobic polymer, optionally also including a hydrophilic or hydrophobic polymer composition, and pharmaceutically acceptable excipients.

(2) Transferring the weighed ingredients from step (1) excluding a lubricant to the product bowl of a system of the type Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL) and pre-heating by fluidization at an inlet air temperature of about 30-40 °C and flow rate of about 15-25 scfm (standard cubic feet per minute) for about 2-5 min.

(3) Granulating the pre-heated material mix from step (2) under fluidization with a granulation fluid in a top-spray mode. The granulation fluids are mainly selected from purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a hydrophilic polymer composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a hydrophilic or hydrophobic polymeric composition, or a solution of a hydrophilic or hydrophobic polymeric composition in a chlorinated solvent or in a ketone. The granulation is conducted at an inlet air temperature of about 30-60 °C and flow rate of about 15-25 scfm.

(4) Drying the granulation from step (3) under fluidization at an inlet air temperature of about 30-60 °C and flow rate of about 15-25 scfm.

(5) Milling and sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Optionally, blending the sieved granulation from step (5) with a lubricant, *e.g.*, in Maxiblend V-shell blender with a 0.5-, 1-, or 2-qt V-shell, for about 5-15 min., forming a uniformly lubricated dry mix ready for compression.

(7) Optionally, passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 13 ***Production of Bioadhesive Carbidopa Trilayer Extended Release Tablets***

Bioadhesive carbidopa trilayer tablets are produced with manual compression. The production processes included the following:

(1) Weighing of a controlled-release formulation of carbidopa produced with low-shear or high-shear granulation method as described in Examples 5 and 6, respectively.

(2) Weighing of one or more bioadhesive compositions produced with low-shear or high-shear, or fluidized bed granulation methods as described in Examples 7 and 8, and 9, respectively.

(3) Blending the bioadhesive compositions from step (2) with one or more hydrophilic polymers in a cylindrical vessel by hand, or in Hobart Mixer type, or in Maxiblend V-shell type blender, for about 5-15 min.

(4) Blending the bioadhesive composition blend from step (3) with a lubricant in a cylindrical vessel by hand, or in Hobart Mixer type, or in Maxiblend V-shell type blender, for about 5-10 min.

Trilayer tablets are produced using a single-station manual tablet press, *e.g.*, GlobePharma Manual Tablet Compaction Machine MTCM-I (GlobePharma, New Brunswick, NJ), equipped with adequate die and punch set. The compression process comprises:

(5) Adding the fist lubricated bioadhesive layer blend from step (4) above into the die cavity, followed by manually tapping it, *e.g.*, using a stainless steel spatula.

(6) Adding the carbidopa controlled release granulation layer blend from step (5) into the die cavity, followed by manually tapping it together with the first layer using a stainless steel spatula.

(7) Adding the second lubricated bioadhesive layer blend from step (4) into the die cavity.

(8) Pre-compressing the three layers together at a pressure ranging from about 250 to 500 pounds per square inch (psi) and a compression time of about 2 to 4 seconds.

(9) Compressing the pre-compacted layers together at a pressure ranging from about 1000 to 4000 pounds per square inch (psi) and a compression time of about 2 to 4 seconds.

Example 14 ***Production of Carbidopa Trilayer Extended Release Tablets***

Carbidopa trilayer tablets are produced with manual compression. The production processes included the following:

(1) Weighing of a controlled-release formulation of carbidopa produced with low-shear or high-shear granulation method as described in Examples 5 and 6, respectively.

(2) Weighing of one or more non-bioadhesive compositions produced with low-shear, high-shear, or fluidized bed granulation methods as described in Examples 9, 10, and 12, respectively.

(3) Blending the composition from step (2) with one or more hydrophilic polymers in a cylindrical vessel by hand, or in a Hobart Mixer type mixer, or in Maxiblend V-shell type blender, for about 5-15 min.

(4) Blending the composition blend from step (3) with a lubricant in a cylindrical vessel by hand, or in Hobart Mixer type mixer, or in Maxiblend V-shell type blender, for about 5-10 min. The lubricated composition blend is used as upper and lower backing layers in a trilayer tablet.

Trilayer tablets are produced using a single-station manual tablet press, *e.g.*, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set. The compression process comprises:

(5) Adding the fist lubricated backing layer blend from step (4) into the die cavity, followed by manually tapping it, *e.g.*, using a stainless steel spatula.

(6) Adding the carbidopa controlled release granulation layer blend from step (1) into the die cavity, followed by manually tapping it together with the first layer, *e.g.*, using a stainless steel spatula.

(7) Adding the second lubricated backing layer blend from step (4) into the die cavity.

(8) Pre-compressing the three layers together at a pressure ranging from about 250 to 500 pounds per square inch (psi) and a compression time of about 2 to 4 seconds.

(9) Compressing the pre-compacted layers together at a pressure ranging from about 1000 to 4000 pounds per square inch (psi) and a compression time of about 2 to 4 seconds.

Example 15 ***Production of Bioadhesive Carbidopa Longitudinally Compressed Extended Release Tablets***

Bioadhesive carbidopa longitudinally compressed tablets (LCTs) are produced with manual compression. Each tablet comprises a longitudinally compressed single layer, having a cross-section in the shape of a circle, an oval, *etc.* The tablet is sealed peripherally with an inner layer of an impermeable hydrophobic polymer and an outer layer of a bioadhesive

polymeric composition, preferably a SPHEROMER™ III composition. The two ends of the tablet were not sealed, and provide the only passageways for drug release.

The production processes comprises:

(1) Weighing of a controlled-release formulation of carbidopa produced with low-shear or high-shear granulation method as described in Examples 5 and 6, respectively.
(2) Pre-compressing the granulation from step (1) using a single-station manual tablet press, *e.g.*, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set, at about 200-300 pounds per square inch (psi) for about 2-4 seconds.
(3) Compressing the pre-compacted tablet from step (2) at about 500-1500 pounds per square inch (psi) for about 2-4 seconds.
(4) Coating the LCTs from step (3) with a hydrophobic polymer composition in a pan coater, *e.g.*, Labcoat M Tablet Coating System (O'Hara Technologies Inc., Richmond Hill, Ontario, Canada).
(5) Optionally, coating the tablets from step (4) with a bioadhesive polymer composition, preferably a SPHEROMER™ III composition, *e.g.*, in Labcoat M Tablet Coating System.
(6) Removing / cutting the inner and outer coating layers from the two ends of tablet, *e.g.*, by a rotary micro-chopper blade, or a laser.

Example 16 ***Production of Carbidopa Pellets with Granulation-Extrusion-Spheronization --p***

Carbidopa pellets are produced with granulation-extrusion-spheronization. The production processes included the following:

(1) Weighing carbidopa, optionally a bioadhesive polymer composition, such as SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof, and pharmaceutically acceptable excipients.
(2) Blending of the weighed ingredients of step (1) in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for about 5-15 min., forming a dry mix.
(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluids are mainly selected from purified

water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone.

(4) Extruding the wet granulation from step (3) through the screen of a screen-type extruder, *e,g,*, Caleva Model 20 (or Model 25) Extruder, operating at about 10-25 rpm, and forming breakable wet strands, the extrudate. The screen aperture is 0.8, 1, or 1.5 mm.

(5) Spheronizing the extrudate from step (4) in a spheronizer, *e.g.* Caleva Model 250, equipped with a 2.5-mm spheronization plate, operating at about 1000-2000 rpm for about 5-10 min., and forming spheronized pellets.

(6) Drying the spheronized pellets from step (5) in a fluidized bed drier, *e.g.*, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of about 100-300 lpm (liters per minute) and an inlet air temperature of about 40-50 °C.

(7) Screening and classifying the dried pellets from step (6), *e.g.*, through stainless steel sieves, U.S. standard mesh sizes 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 45, and/or 60, using a mechanical sieve shaker, *e.g.*, W.S. Tyler Sieve Shaker Ro-Tap Rx-29. Particle size and distribution of pellet formulations were analyzed, and classified pellets ranging from 0.25 mm (mesh # 60) to 2 mm (mesh # 10) were used for film coating or in other dosage form preparations.

Example 17 ***Film coating of Carbidopa Pellets --p***

Carbidopa pellets are film-coated with a layer of release rate controlling polymer(s), such as Eudragit® RL 100, Eudragit® RS 100, or mixtures thereof, and optionally with a top-layer of a bioadhesive polymer composition such as SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof. Optionally, pellets are film-coated with an additional layer of a non-functional polymer, such as Eudragit® E 100, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and polyvinyl alcohol. Polymers are dissolved in different solvent systems depending on their solubility characteristics. The film coating is performed in a fluidized bed coater, *e.g.*, Vector MFL.01 Micro Batch Fluid Bed System or a Fluid Air Fluid Bed System Model 5, equipped with a Wurster insert,

operating at an inlet air temperature of about 30-50 °C.

Example 18 ***In vitro Dissolution of Carbidopa Formulations***

The *in vitro* dissolution profile of carbidopa formulations are obtained under simulated gastric conditions. The dissolution tests are performed in 900 mL of either of 0.1 N HCl – pH 1.2, phosphate buffer saline (PBS) - pH 4.5, or sodium acetate buffer - pH 4.5 solutions in a USP II apparatus at a temperature of 37±0.5 °C. The paddle speed was set at 50 rpm. Samples of dissolution media are collected at predetermined intervals and analyzed by either HPLC or UV spectrophotometry.

Example 19 ***Bioadhesive Carbidopa 100 mg Trilayer Extended Release Tablets, Lot # 607-015***

Bioadhesive carbidopa trilayer tablets were produced in accordance with the method described in Example 13. These tablets comprise an active controlled release (CR) layer laminated between two passive bioadhesive layers. Both the CR and bioadhesive layer granulations were screened through a U.S. Std. mesh # 40 sieve. The weight and composition of the CR and bioadhesive layers are given in Table 19.

Table 19. Weight and Composition of Controlled Release and Biaodhesive Layers of Carbidopa 100 mg Trilayer Tablet, Lot # 607-015

Controlled Release Layer		
Ingredients	**Weight %**	**Weight (mg)**
Carbidopa, Monohydrate	30.86	108.0
Fumaric Acid	42.86	150.0
Hypromellose 2208, 100 cps	19.89	69.6
Hypromellose 2910, 5 cps	5.00	17.5
Hypromellose 2208, 4000 cps	1.00	3.5
Magnesium Stearate	0.28	1.0
Butylated Hydroxytoluene	0.11	0.4

Total	100.0	350.0
Bioadhesive Layer		
Ingredients	**Weight %**	**Weight (mg)**
SPHEROMER™ III Granulation	75.0	187.5
Poly(FASA) Granulation	24.6	61.5
Magnesium Stearate	0.4	1.0
Total	100.0	250.0

CR layer granulation and bioadhesive layer granulations were blended separately with magnesium stearate in a cylindrical vessel mounted on an ATR type rotator for about 5 min. An about 0.3" x 0.9" capsule-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-I. The CR and two bioadhesive layers were pre-compressed together at a pressure of about 500 psi (pound per square inch) for about 2 seconds and then pressed at about 4000 psi for about 2 seconds.

Example 20 ***In vitro Dissolution of Bioadhesive Carbidopa 100 mg Trilayer Tablets, Lot # 607-015***

The *in vitro* dissolution profile of bioadhesive carbidopa trilayer tablets, containing 100 mg carbidopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of both 0.1 N HCl – pH 1.2 and phosphate buffer saline (PBS) - pH 4.5 solutions in a USP II apparatus at a temperature of about 37±0.5 °C. The paddle speed was set at about 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. See Figure 51 for the dissolution profiles of carbidopa obtained from HPLC analysis.

Example 21 ***Bioadhesive Carbidopa 100 mg Trilayer Extended Release Tablets, Lot # 607-016***

Bioadhesive carbidopa trilayer tablets were produced in accordance with the method described in Example 13. These tablets comprise an active controlled release (CR) layer laminated between two passive bioadhesive layers. Both the CR and bioadhesive layer

granulations were screened through a U.S. Std. mesh # 40 sieve. The weight and composition of the CR and bioadhesive layers are given in Table 21.

Table 21. Weight and Composition of Controlled Release and Biaodhesive Layers of Carbidopa 100 mg Trilayer Tablet, Lot # 607-016

Controlled Release Layer		
Ingredients	**Weight %**	**Weight (mg)**
Carbidopa, Monohydrate	26.02	108.0
Fumaric Acid	36.14	150.0
Hypromellose 2208, 100 cps	16.77	69.6
Succinic Acid	15.66	65.0
Hypromellose 2910, 5 cps	4.22	17.5
Hypromellose 2208, 4000 cps	0.84	3.5
Magnesium Stearate	0.25	1.0
Butylated Hydroxytoluene	0.10	0.4
Total	100.0	415.0
Bioadhesive Layer		
Ingredients	**Weight %**	**Weight (mg)**
SPHEROMER™ III Granulation	75.0	187.5
Poly(FASA) Granulation	24.6	61.5
Magnesium Stearate	0.4	1.0
Total	100.0	250.0

CR layer granulation and bioadhesive layer granulations were blended separately with magnesium stearate in a cylindrical vessel mounted on an ATR type rotator for about 5 min. An about 0.3" x 0.9" capsule-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-I. The CR and two bioadhesive layers were pre-compressed together at a pressure of about 500 psi (pound per square inch) for about 2 seconds, and then pressed at about 4000 psi for about 2 seconds.

Example 22 ***In vitro Dissolution and In vivo Pharmacokinetic Performance of Bioadhesive Carbidopa 100 mg Trilayer Tablets, Lot # 607-016***

The *in vitro* dissolution profile of bioadhesive carbidopa trilayer tablets, containing 100 mg carbidopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of both 0.1 N HCl – pH 1.2 and phosphate buffer saline (PBS) - pH 4.5 solutions in a USP II apparatus at a temperature of about 37±0.5 °C. The paddle speed was set at about 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. See Figure 52 for the dissolution profiles of carbidopa obtained from HPLC analysis.

The *in vivo* performance of bioadhesive carbidopa trilayer tablets was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed state. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 53 shows the plasma concentration profiles of cabidopa in the fed state. The pharmacokinetic data including the area under the plasma carbidopa vs. time curve (AUC), maximum concentration (Cmax) and time required to achieve C_{max} (T_{max}) are provided in Table 22.

Table 22. Pharmacokinetic Data for Bioadhesive Carbidopa 100 mg Trilayer Tablets, Lot # 607-016, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Fasting Period	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
Fed	6,160	590	7.8

Example 23 ***Fluidized Bed Granulation of a non-Bioadhesive Hydrophobic Polymer with Bioadhesive Polymers --p***

Granules are produced with fluidized bed granulation method, *e.g.*, comprising:

(1) Weighing a non-bioadhesive hydrophobic polymer, optionally a hydrophilic polymer composition, and pharmaceutically acceptable excipients.

(2) Transferring the weighed ingredients from step (1) excluding a lubricant to, for example, the product bowl of a Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL) and pre-heating by fluidization at an inlet air temperature of about 30-40°C and flow rate of about 15-25 scfm (standard cubic feet per minute) for about 2-5 min.

(3) Granulating the pre-heated material mix from step (2) under fluidization with a granulation fluid, *e.g.*, in a top-spray mode. The granulation fluid is mainly an alcoholic solution of a bioadhesive polymer composition, such as SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ II, SPHEROMER™ III, SPHEROMER™ IV polymers, or mixtures thereof. The granulation is conducted, for example, at an inlet air temperature of about 30-40°C and flow rate of about 15-25 scfm.

(4) Drying the granulation from step (3) under fluidization, *e.g.*, at an inlet air temperature of about 30-35°C and flow rate of about 15-25 scfm.

(5) Milling and sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Optionally blending the sieved granulation from step (5) with a lubricant, *e.g.*, in a V-shell blender for about 5-15 min, forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 24 ***Fluidized Bed Granulation of Ethylcellulose with Bioadhesive SPHEROMER™ III Polymer and Succinic Acid --p***

Ethylcellulose granules are produced by fluidized bed granulation method, comprising:

(1) Weighing 1000 grams of ethylcellulose (ETHOCEL™ Standard 20 Premium) 42.5 grams of SPHEROMER™ III, and about 7.5 grams of succinic acid.

(2) Dissolving SPHEROMER™ III and succinic acid from step (1) in about 1000 mL of methyl alcohol.

(3) Transferring ethylcellulose from step (1) to the product bowl of, for example, a Fluid Air Fluid Bed System, Model 5 (Fluid Air Inc., Aurora, IL) and pre-heating by fluidization at an inlet air temperature of about 35°C and flow rate of about 15 scfm (standard cubic feet per minute) for about 2 min.

(4) Granulating the pre-heated ethylcellulose from step (3) with the spray solution from step (2), *e.g.*, at an inlet air temperature of about 35°C and flow rate of about 15-17 scfm in a top spray mode.

(5) Drying the granulation from step (4) under fluidization, *e.g.*, at an inlet air temperature of about 35°C and flow rate of about 17 scfm.

(6) Sieving/sifting the granulation through a U.S. Std. mesh # 20 screen.

The particle size distribution of dried granulation produced by this method before and after sieving is determined as shown in Figure 56.

Example 25 ***Fluidized Bed Granulation of a non-Bioadhesive Hydrophilic Polymer with Bioadhesive Polymers***

Granules are produced with fluidized bed granulation method, comprising:

(1) Weighing a non-bioadhesive hydrophilic polymer, optionally a hydrophobic polymer composition, and pharmaceutically acceptable excipients.

(2) Transferring the weighed ingredients from step (1) excluding a lubricant to the product bowl of, for example, a Vector Micro Flo-Coater MFL-01 (Vector Corporation, Marion, IA) and pre-heating by fluidization at an inlet air temperature of about 30-40°C and flow rate of about 50-200 lpm (liters per minute) for about 2-5 min.

(3) Granulating the pre-heated material mix from step (2) under fluidization with a granulation fluid, *e.g.*, in a top-spray mode. The granulation fluid is mainly an alcoholic solution of a bioadhesive polymer composition, such as SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ II, SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof. The granulation is conducted, for example, at an inlet air temperature of about 30-40°C and flow rate of about 50-200 lpm.

(4) Drying the granulation from step (3) under fluidization at an inlet air temperature of about 30-35°C and flow rate of about 50-200 lpm.

(5) Milling and sieving the ground material, *e.g.*, through a U.S. Std. mesh # 20 screen.

(6) Optionally blending the sieved granulation from step (5) with a lubricant, *e.g.*, in a V-shell blender for about 5-15 min, forming a uniformly lubricated dry mix ready for compression.

(7) Optionally passing the lubricated dry mix from step (6) through a U.S. Std. mesh # 20 screen.

Example 26 ***Fluidized Bed Granulation of Hydroxypropylcellulose with Bioadhesive SPHEROMER™ III Polymer, Succinic Acid, and Citric Acid***

Hydroxypropylcellulose granules are produced with fluidized bed granulation method, comprising:

(1) Weighing about 60 grams of hydroxypropylcellulose (HPC-H), about 2.7 grams of SPHEROMER™ III, about 3.0 grams of succinic acid, and about 0.3 grams of anhydrous citric acid.

(2) Dissolving SPHEROMER™ III, succinic acid, and citric acid from step (1) in about 150 mL of methyl alcohol.

(3) Transferring hydroxypropylcellulose from step (1) to the product bowl of, for example, a Vector Micro Flo-Coater MFL-01 (Vector Corporation, Marion, IA) and pre-heating by fluidization at an inlet air temperature of about 30°C and flow rate of about 50 lpm (liters per minute) for 2 about min.

(4) Granulating the pre-heated hydroxypropylcellulose from step (3) with the spray solution from step (2), *e.g.*, at an inlet air temperature of about 35°C and flow rate of about 50-170 lpm in a top spray mode.

(5) Drying the granulation from step (4) under fluidization, *e.g.*, at an inlet air temperature of about 35°C and flow rate of about 130 lpm.

(6) Sieving/sifting the granulation, *e.g.*, through a U.S. Std. mesh # 20 screen.

Example 27 ***Exemplary Levodopa-Carbidopa Extended Release Tablets – Formula A***

An exemplary dosage form of the subject Levodopa-Carbidopa extended release tablets was manufactured as follows: First, about 80.0 g of anhydrous lactose, 80.0 g of micronized levodopa, 21.6 g of carbidopa, 12.0 g of crospovidone, 21.2 g of anhydrous citric acid, and 2.0 g of povidone K-25 were mixed in a Hobart mixer for 5 minutes. The blend was granulated with a binder solution of povidone K-25 in methyl alcohol in the Hobart mixer. The wet granulation was dried in the Vecor MFL.01 fluid bed dryer to a moisture content of

not more than 0.5%. The granulation was sized through a #40 screen and mixed in a V-shell blend with the 12.0 g of crospovidone for 5 minutes, and lubricated with 1.0 g of magnesium stearate. This blend was used for immediate release layer.

Next, a controlled release layer granulation was prepared as follows: about 121.0 g of fumaric acid, 147.9 g of micronized levodopa, 39.9 g of carbidopa monohydrate, 9.9 g of hypromellose 2208, 4000 cps, 6.0 g of Hypromellose 2910, 5 cps, were mixed in a Hobart mixer for 5 minutes. The powder blend was granulated with a binder solution of Hypromellose 2910, 5 cps, and butylated hydroxytoluene in methyl alcohol in the Hobart mixer. The wet granulation was dried in the Vecor MFL.01 fluid bed dryer to a moisture content of not more than 0.5%. The granulation was sized through a #20 screen and lubricated in a V-shell blend with 1.4 g of magnesium stearate.

Next, the bioadhesive backing layer granulation was prepared as follows: about 290.5 g of Spheromer III, 31.8 g of hydroxypropyl cellulose, and 14.0 g of anhydrous citric acid were mixed in a Hobart mixer for 5 minutes, and the blend was granulated with a binder solution of hydroxypropyl cellulose in methylene chloride. The wet granulation was dried in the Vecor MFL.01 fluid bed dryer until residual solvent levels were achieved. Separately, about 155.0 g of Spheromer I, 15.4 g of hydroxypropyl cellulose were mixed in a Hobart mixer for 5 minutes, and the blend was granulated with a binder solution of hydroxypropyl cellulose in dehydrated alcohol. The wet granulation was dried in the Vecor MFL.01 fluid bed dryer until residual solvent levels were achieved. The Spheromer I (72.0) and Spheromer III (217.7 g) granulation were mixed in a blender and lubricated with magnesium stearate (0.6 g) for 5 minutes.

Table 27 below lists the components of the different tablet layers in a representative lot.

Table 27. Levodopa-Carbidopa XL Tablet, 200 mg / 50 mg (Bioadhesive) (Lot # 611-032)

Tablet Layer	Component	Amount Per Batch (g)
Immediate Release Drug Layer	Levodopa, Micronized	80.0
	Carbidopa, Monohydrate	21.6†
	Citric Acid, Anhydrous	21.2
	Anhydrous Lactose	80.0

	Crospovidone (Polyplasdone® XL)	24.0
	Povidone (Plasdone K-25)	12.0
	Butylated Hydroxytoluene	0.2
	Magnesium Stearate	1.0
	Methyl Alcohol*	*
Extended Release Drug Layer	Levodopa, Micronized	147.9
	Carbidopa, Monohydrate	39.9‡
	Fumaric Acid	121.0
	Hypromellose 2910, 5 cps	29.6
	Hypromellose 2208, 4000 cps	9.9
	Butylated Hydroxytoluene	0.3
	Magnesium Stearate	1.4
	Methyl Alcohol*	*
Backing Layer (Bioadhesive)	Spheromer™ I	155.0
	Spheromer™ III	290.5
	Hydroxypropyl cellulose (Klucel EF Pharm)	68.7
	Citric Acid, Anhydrous	14.0
	Magnesium Stearate	0.6
	Alcohol, Dehydrated*	*
	Methylene Chloride*	*
Total		1118.8

* Solvents used as process aid, removed during processing.

† Equivalent to 20.0 g carbidopa anhydrous

‡ Equivalent to 36.9 g carbidopa anhydrous

Next, the immediate release, controlled release, and bioadhesive backing layer compositions were compressed into four-layer tablets on a Globe Pharma MTCM 1 press using 0.328" x 0.897" capsule toolings. First, 250 mg of backing layer granulation was added to the die cavity, then 355 mg of controlled release granulation was added and pre-compressed, then 250 mg of backing layer was added, and finally, 150 mg of immediate release granulation was added. The multilayer tablets were compressed at pre-compression force if 500 psi for 2 seconds, followed by main compression at a target pressure of 4000 psi

for 2 seconds.

Specific equipments and conditions used herein are for illustrative purpose only, and are not intended to be limiting.

Figure 57 is a schematic drawing (not necessarily to scale) showing a possible drug release mechanism for the subject Levodopa-Carbidopa extended release (XL) tablets. Specifically, the extended / controlled release layer is sandwiched between two backing layers, which backing layers may or may not contain bioadhesive materials (see Examples 27 and 28). On top of one (or both) of the backing layers is an immediate release layer that quickly disintegrates and dissolves. Drug release from the extended / controlled release layer, however, is much slower. Due to the presence of the inactive backing layers, drug release from the extended / controlled release layer begins around the exposed edge or side of the sandwiched-in extended / controlled release layer, and gradually goes towards the inner portion of the extended / controlled release layer.

Optionally, the thickness and density of the extended / controlled release layer can be designed such, that at a certain point, erosion of the extended / controlled release layer will result in the breaking of the tablet in two (not necessarily equal halves), thus creating larger erosion surfaces. The increased drug release rate towards the end of the drug release period can produce a delayed or ascending release profile, which may be desirable in certain embodiments (see above).

Release profile studies were performed using the resulting tablet. In an exemplary study, six tablets from Lot # 611-032 were dissolved in 0.1 N HCl using USP Paddle method at 50 rpm. The results for the 6 individual tablets, as well as the average, over a time period of 20 hours are shown in Figure 13. It is apparent that remarkably consistent results were achieved among the different tablets tested.

Example 28 ***Exemplary Levodopa-Carbidopa Extended Release Tablets – Formula B***

Another exemplary dosage form of the subject Levodopa-Carbidopa extended release tablets was manufactured as follows: First, about 80.0 g of anhydrous lactose, 80.0 g of micronized levodopa, 21.6 g of carbidopa, 12.0 g of crospovidone, 21.2 g of anhydrous citric acid, and 2.0 g of povidone K-25 were mixed in a Hobart mixer for 5 minutes. The blend was granulated with a binder solution of povidone K-25 in methyl alcohol in the Hobart mixer. The wet granulation was dried in the Vecor MFL.01 fluid bed dryer to a moisture content of

not more than 0.5%. The granulation was sized through a #40 screen and mixed in a V-shell blend with 12.0 g of crospovidone for 5 minutes, and lubricated with 1.0 g of magnesium stearate. This blend was used for immediate release layer.

Next, a controlled release layer granulation was prepared as follows: about 121.0 g of fumaric acid, 147.9 g of micronized levodopa, 39.9 g of carbidopa monohydrate, 9.9 g of Hypromellose 2208, 4000 cps, 6.0 g of Hypromellose 2910, 5 cps, were mixed in a Hobart mixer for 5 minutes. The powder blend was granulated with a binder solution of Hypromellose 2910, 5 cps, and butylated hydroxytoluene in methyl alcohol in the Hobart mixer. The wet granulation was dried in the Vecor MFL.01 fluid bed dryer to a moisture content of not more than 0.5%. The granulation was sized through a #20 screen and lubricated in a V-shell blend with 1.4 g of magnesium stearate.

Next, the backing layer granulation was prepared as follows: about 500.0 g of Ethocel Std. 20 Premium was added to the bowl of the Fluid Bed Model 5 unit. About 25.0 g of Ethocel Std. 10 Premium was dissolved in a mixture of dehydrated alcohol and purified water to form a binder solution. This binder solution was sprayed onto the Ethocel Std 20 Premium and dried. The dried material was sifted through a #20 screen. The dried granulation was blended with 10.0 g of Hypromellose 2208, 100 K in a V-shell blender for 10 minutes, and subsequently lubricated with 1.6 g of magnesium stearate for 5 minutes.

Table 28 below lists the components of the different tablet layers in a representative lot.

Table 28. Levodopa – Carbidopa XL Tablet, 200 mg/50 mg (Non-bioadhesive) (Lot # 710-010)

Tablet Layer	**Component**	**Amount Per Batch Bioadhesive (Formulation K) Weight (g)**
Immediate Release Drug Layer	Levodopa, Micronized	80.0
	Carbidopa, Monohydrate	21.6†
	Citric Acid, Anhydrous	21.2
	Anhydrous Lactose	80.0
	Crospovidone (Polyplasdone® XL)	24.0
	Povidone (Plasdone K-25)	12.0
	Butylated Hydroxytoluene	0.2

	Magnesium Stearate	1.0
	Methyl Alcohol*	*
Extended Release Drug Layer	Levodopa, Micronized	147.9
	Carbidopa, Monohydrate	39.9‡
	Fumaric Acid	121.0
	Hypromellose 2910, 5 cps	29.6
	Hypromellose 2208, 4000 cps	9.9
	Butylated Hydroxytoluene	0.3
	Magnesium Stearate	1.4
	Methyl Alcohol*	*
Backing Layer (Non-bioadhesive)	Ethylcellulose (*Ethocel™ Std. 10 Premium*)	25.0
	Ethylcellulose (*Ethocel™ Std. 20 Premium*)	500.0
	Methylcellulose (*Methocel™K100M*)	10.0
	Magnesium Stearate	1.6
Total		1126.6

* Solvents used as process aid, removed during processing.

† Equivalent to 20.0 g carbidopa anhydrous.

‡ Equivalent to 36.9 g carbidopa anhydrous.

Next, the immediate release, controlled release, and backing layer compositions were compressed into four-layer tablets on a Globe Pharma MTCM 1 press using 0.328" x 0.897" capsule toolings. First, 250 mg of backing layer granulation was added to the die cavity, then 358 mg of controlled release granulation was added and pre-compressed, then 250 mg of backing layer was added, and finally, 151 mg of immediate release granulation was added. The multilayer tablets were compressed at pre-compression force if 500 psi for 2 seconds, followed by main compression at a target pressure of 4000 psi for 2 seconds. See Figure 57 for a representative tablet produced by the subject method.

Specific equipments and conditions used herein are for illustrative purpose only, and are not intended to be limiting.

Release profile studies were performed using the resulting tablets. In an exemplary study, six tablets from Lot No. 710-010 were dissolved in 0.1 N HCl using USP Paddle method at 50 rpm. The results for the 6 individual tablets, as well as the average, over a time period of 20 hours are shown in Figure 59. It is apparent that remarkably consistent results

were achieved among the different tablets tested.

Equivalents:

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All patents, publications, and other references cited above are hereby incorporated by reference in their entirety.

We Claim:

1. A pharmaceutical composition comprising a decarboxylase enzyme inhibitor formulated to provide an effective plasma concentration of the decarboxylase enzyme inhibitor over a predetermined extended period of time after the administration of the pharmaceutical composition to the patient.

2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises:

   (1) one or more bioadhesive layers;

   (2) one or more bioadhesive compositions incorporated in the pharmaceutical composition, or,

3. The pharmaceutical composition of claim 1 or 2, wherein the pharmaceutical composition is substantially free of levodopa.

4. The pharmaceutical composition of any of claims 1-3, wherein the pharmaceutical composition is substantially free of immediate release formulation of decarboxylase enzyme inhibitor.

5. The pharmaceutical composition of any of claims 1-4, wherein less than 25% of the decarboxylase enzyme inhibitor in the pharmaceutical composition is released within the first hour after administration to the patient.

6. The pharmaceutical composition of any of claims 1-5, wherein less than 25% of the decarboxylase enzyme inhibitor in the pharmaceutical composition is released within the first hour after release of the decarboxylase inhibitor commences.

7. The pharmaceutical composition of any of claims 1-6, wherein the decarboxylase enzyme inhibitor is formulated to provide a constant effective plasma concentration starting at least about 4 hours after administration to the patient.

8. The pharmaceutical composition of any of claims 1-7 wherein the predetermined extended period of time is about 7-14 hours, 8-14 hours, or about 9-13 hours, or about 10-12 hours, or about 11 hours.

9. The pharmaceutical composition of any of claims 1-8, wherein the decarboxylase enzyme inhibitor is released at a substantially constant rate over the predetermined extended period of time.

10. The pharmaceutical composition of any of claims 1-9, wherein the decarboxylase

enzyme inhibitor is formulated in a partially exposed core between two bioadhesive layers.

11. The pharmaceutical composition of any of claims 1-10, wherein the target absorption site is proximal small intestine.

12. The pharmaceutical composition of any of claims 1-11, further comprising a sleep-inducing agent.

13. The pharmaceutical composition of any of claims 1-12, further comprising one or more of: a dopaminergic and anti-cholinergic agent selected from: amantadine; an anti-cholinergic agent selected from: trihexyphenidyl, benztropine, ethopropazine, or procyclidine; a dopamine agonist selected from: apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, or ropinirole; a MAO-B (monoamine oxidase B) inhibitor selected from: selegiline or deprenyl; a COMT inhibitor selected from: CGP-28014, entacapone, or tolcapone; a muscle relaxant baclofen; a sedative Clonazepam; an anticonvulsant agent carbamazepine; a dopamine reuptake inhibitor tetrabenazine; a dopamine blocker haloperidol; a β-blocker selected from: propranolol; a carbonic anhydrase inhibitor selected from: acetalzolamide or methazolamide; a narcotic agent codeine; a GABAergic agent gabapentin; an alpha antagonist clonidine; a stool softener selected from: bran or psyllium, methylcellulose, polycarbophil, docusate, docusate sodium and casanthranol combination, magnesium hydroxide, magnesium citrate, sorbitol, polyethylene glycol solution, lactulose, lubiprostone or other osmotic or stimulant laxatives, and a natural stool softener; or a dopamine transport inhibitor.

14. The pharmaceutical composition of any of claims 1-13, wherein the decarboxylase enzyme inhibitor is carbidopa, a carbidopa prodrug, benserazide, methylphenidate, or a combination thereof.

15. The pharmaceutical composition of any of claims 1-14, wherein the total dose of the decarboxylase enzyme inhibitor is about 25 – 300 mg, about 50-200 mg, or about 100 mg.

16. The pharmaceutical composition of any of claims 1-15, wherein the one or more bioadhesive layers include bioadhesive materials selected from polyamides, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, polyvinylpyrrolidone, polyglycolides, polyurethanes, polymers of acrylic and methacrylic esters,

polylactides, poly(butyric acid), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends and copolymers thereof.

17. The pharmaceutical composition of any of claims 1-16, wherein the one or more bioadhesive layers include poly(fumaric-co-sebacic) anhydride.

18. The pharmaceutical composition of any of claims 1-17, wherein the one or more bioadhesive layers comprise bioadhesive materials having a catechol moiety.

19. The pharmaceutical composition of claim 18, wherein the bioadhesive materials comprise a mixture of a material and a compound comprising a catechol moiety selected from L-Dopa, D-dopa, dopamine, or carbidopa.

20. The pharmaceutical composition of claim 18 or 19, wherein the bioadhesive materials are selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends, and/or copolymers thereof.

21. The pharmaceutical composition of any of claims 1-20, wherein the one or more bioadhesive layers comprise bioadhesive material covalently functionalized with a catechol moiety.

22. The pharmaceutical composition of claim 21, wherein the catechol moiety is derived from L-dopa, D-dopa, dopamine, or carbidopa.

23. The pharmaceutical composition of any of claims 1-22, wherein the one or more bioadhesive layers comprises an additive that stabilizes the bioadhesive layers from erosion, dissolution or both, wherein at least 50% by weight of a 1 mm thick film of the bioadhesive layers remain after 12 hours in a buffered pH 4.5 dissolution bath.

24. The pharmaceutical composition of any of claims 1-23, wherein the bioadhesive layers comprise an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

25. The pharmaceutical composition of any of claims 1-24, suitable for human treatment, or for veterinary treatment of a non-human mammal.

26. A method of making a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising combining the decarboxylase enzyme inhibitor with one or more bioadhesive layers of any of the pharmaceutical composition of claims 1-25 into a single dosage form.

27. A method of treating a patient suffering from Parkinson's disease and/or another movement disorder, comprising administering to the patient a pharmaceutical composition of any of claims 1-25.

28. The method of claim 27, wherein the pharmaceutical composition is administered before the patient goes to sleep.

29. The method of claim 27, wherein the pharmaceutical composition is administered shortly before, with, or after the patient's last meal before going to sleep.

30. The method of claim 27, further comprising administering a second pharmaceutical composition comprising levodopa or metabolic precursor thereof 6-12 hours thereafter.

31. A packaged pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising:

    (1) a first pharmaceutical composition comprising any of the pharmaceutical compositions of claims 1-25;

    (2) a second pharmaceutical composition comprising levodopa or a metabolic precursor thereof.

32. The packaged pharmaceutical composition of claim 31, wherein the first and/or the second pharmaceutical composition is packaged separately as individual doses.

33. The packaged pharmaceutical composition of claim 32, wherein the package comprises at least one dose each of the first and the second pharmaceutical compositions.

34. The packaged pharmaceutical composition of claims 31-33, wherein the first and the second pharmaceutical compositions are differentiated by color, shape, marking, imprinting, and/or size.

35. The packaged pharmaceutical composition of claims 31-34, further comprising an instruction that instructs a patient to take the first pharmaceutical composition before sleep, and to take the second pharmaceutical composition after waking.

36. The packaged pharmaceutical composition of claims 31-35, which package comprises sufficient doses for treating a patient over a week.

37. A method for the manufacture of granules comprising a bioadhesive polymer, comprising

    i) dissolving a bioadhesive polymer in a solvent to form a solution,

    ii) combining a second polymer with the solution, and,

    iii) evaporating solvent from said solution under conditions that result in the formation of granules.

38. The method of claim 37, wherein the bioadhesive polymer is selected from SPHEROMER™ I[p(FASA) (1:4)], SPHEROMER™ II, SPHEROMER™ III, and SPHEROMER™ IV polymers.

39. The method of claim 37, wherein the second polymer is a hydrophobic polymer.

40. The method of claim 37, wherein the second polymer is a hydrophilic polymer.

41. The method of claim 37, wherein the second polymer is a non-bioadhesive polymer.

42. Bioadhesive granules comprising about 2% to about 20% of a bioadhesive polymer and about 80% to about 98% of a second polymer.

43. The bioadhesive granules of claim 42, wherein the bioadhesive polymer is selected from SPHEROMER™ I [p(FASA) (1:4)], SPHEROMER™ II, SPHEROMER™ III, and SPHEROMER™ IV polymers.

44. The bioadhesive granules of claim 42, wherein the second polymer is a non-bioadhesive polymer.

45. The bioadhesive granules of claim 42, wherein the second polymer is selected from methylcellulose (MC), carboxymethylcellulose (CMC), hydroxyethylcellulose (HEC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP), vinylpyrrolidone/vinyl acetate copolymer, polyethylene oxide (PEO), methacrylic acid copolymers, methacrylic ester copolymers, ammonioalkyl methacrylate copolymers, cellulose acetate, cellulose acetate butyrate, chitin, chitosan, and ethyl cellulose.

46. The bioadhesive granules of claim 42, wherein the granules can be compressed into a solid matrix.

47. A bioadhesive polymer comprising a poly(ethylene-co-maleic anhydride) polymer backbone functionalized with residues of at least one compound comprising:

(a) an aromatic moiety comprising two or more hydroxyl substituents, methoxy substituents, substituents hydrolyzable to hydroxyl substituents, or a combination thereof, and,

(b) a primary or secondary amino moiety.

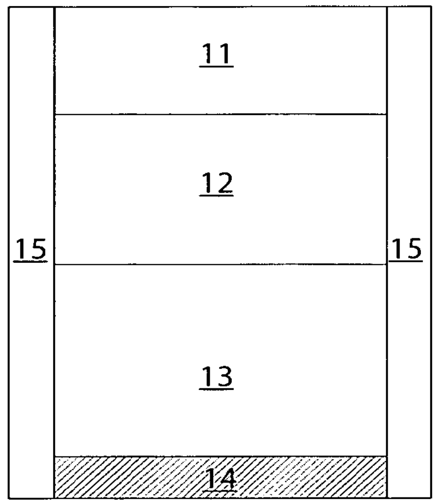


Fig. 1

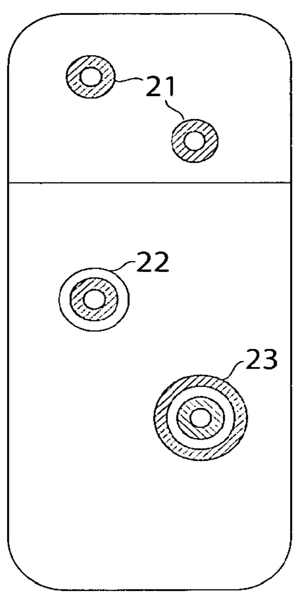


Fig. 2

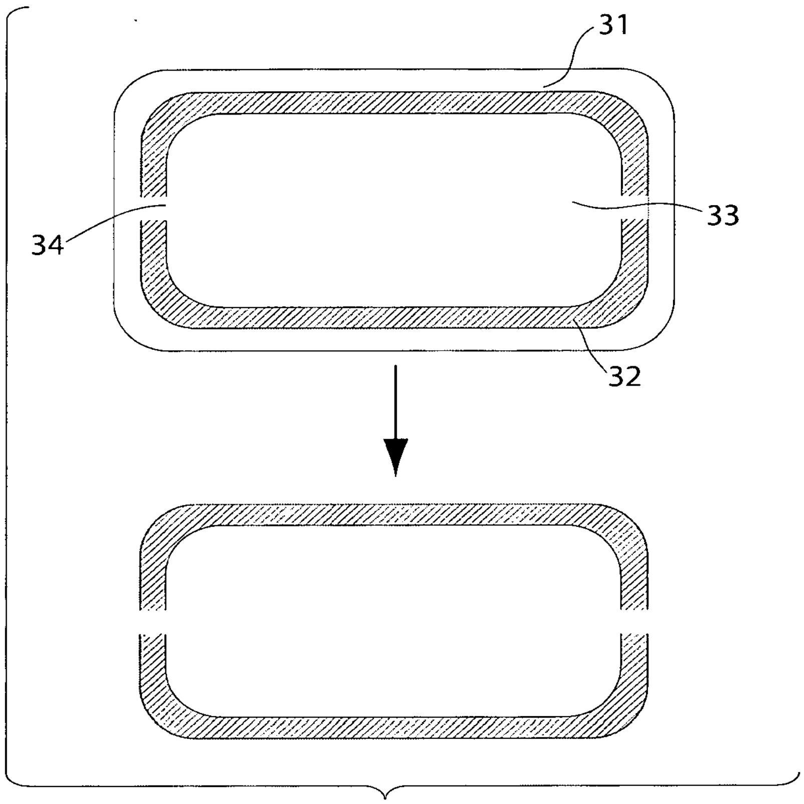


Fig. 3

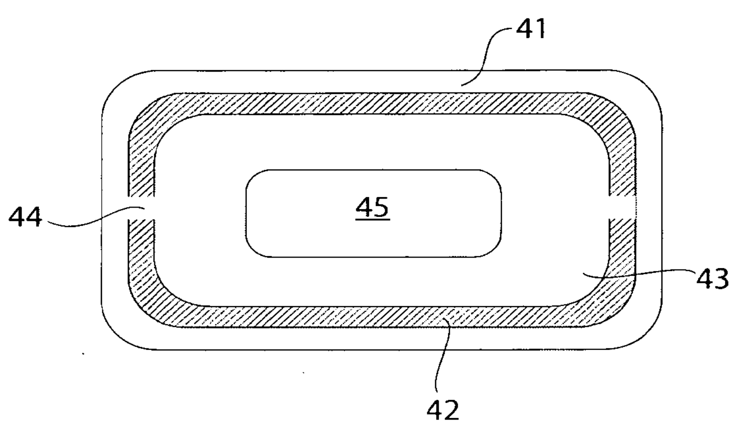


Fig. 4

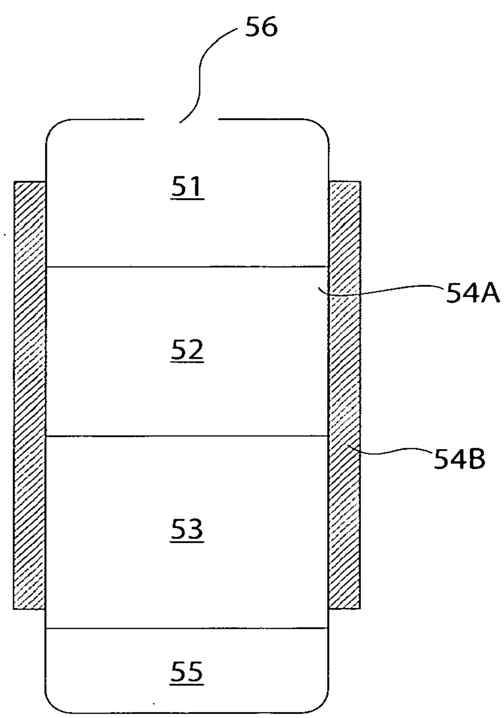


Fig. 5

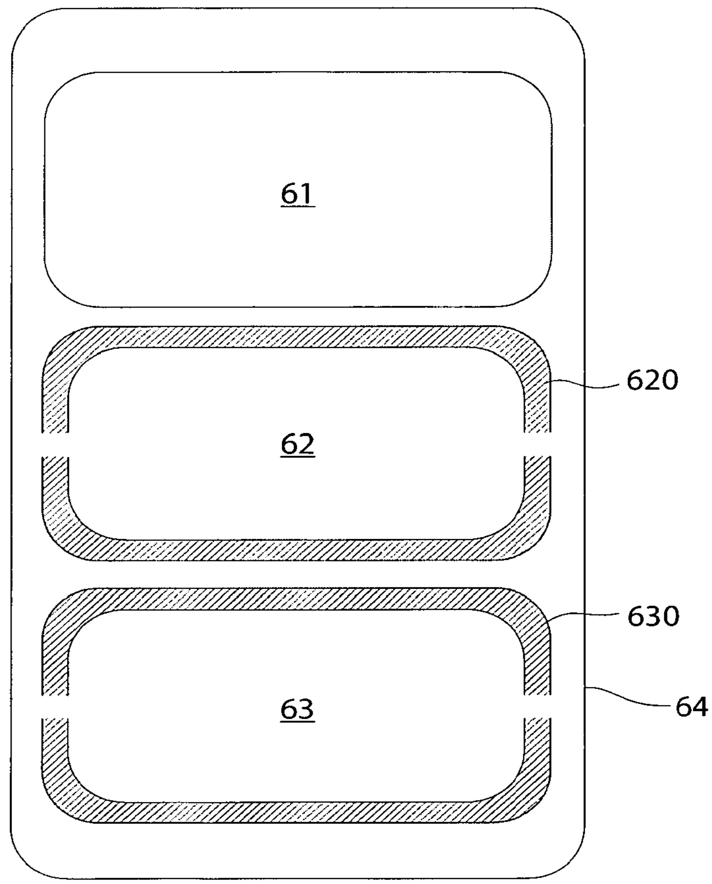


Fig. 6

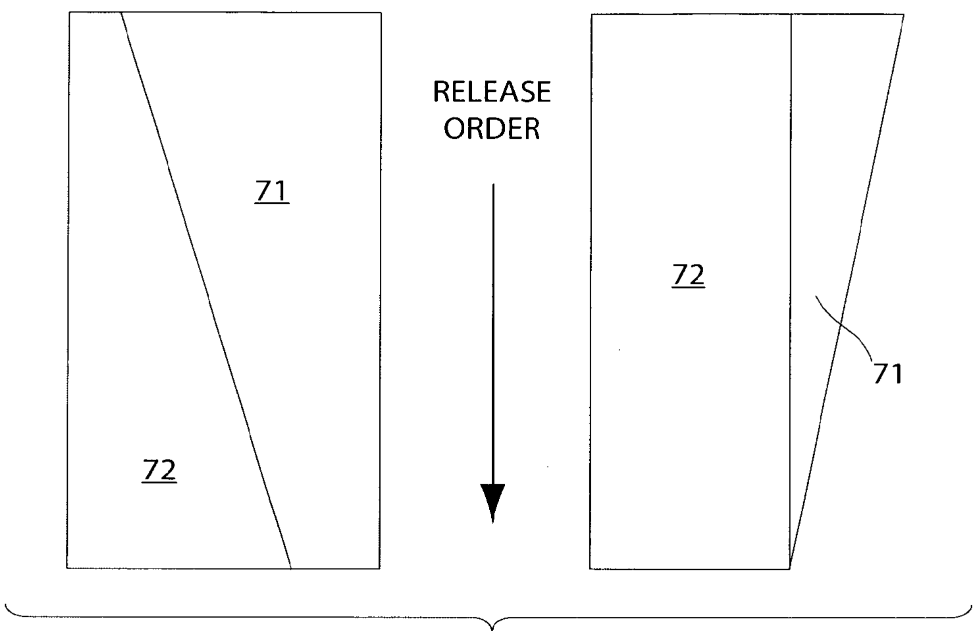


Fig. 7

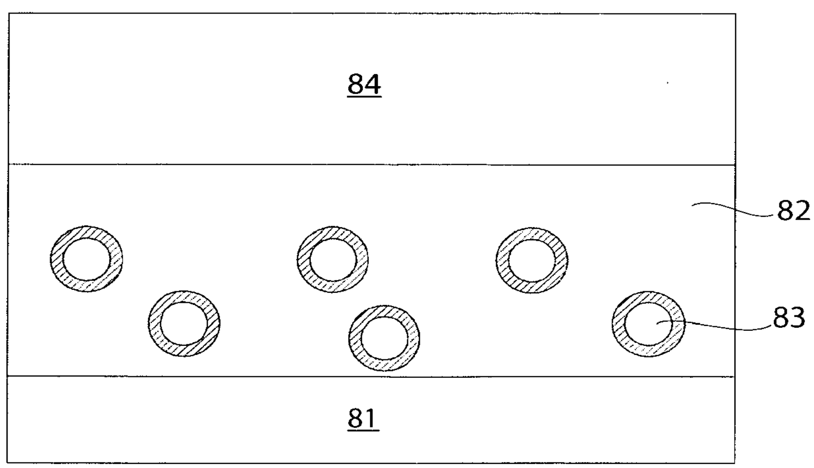


Fig. 8

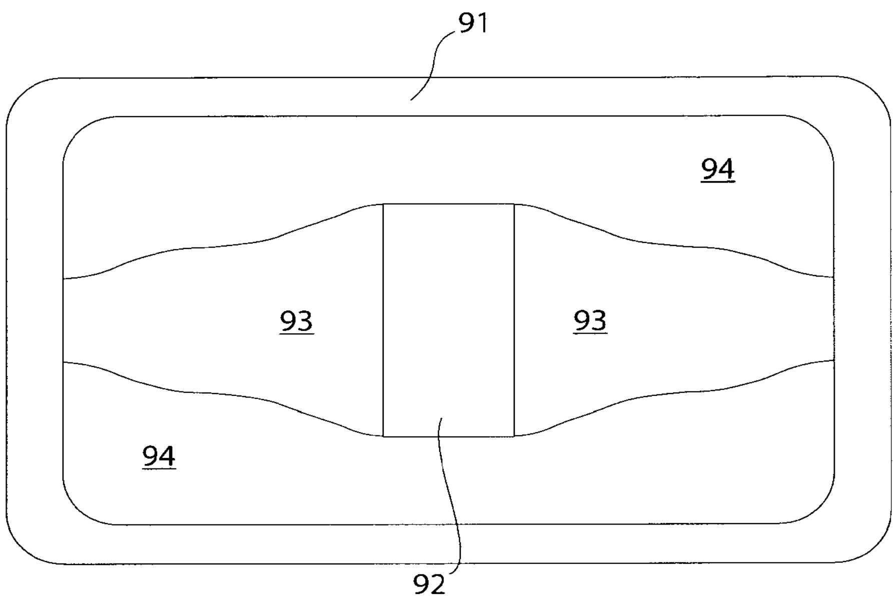


Fig. 9

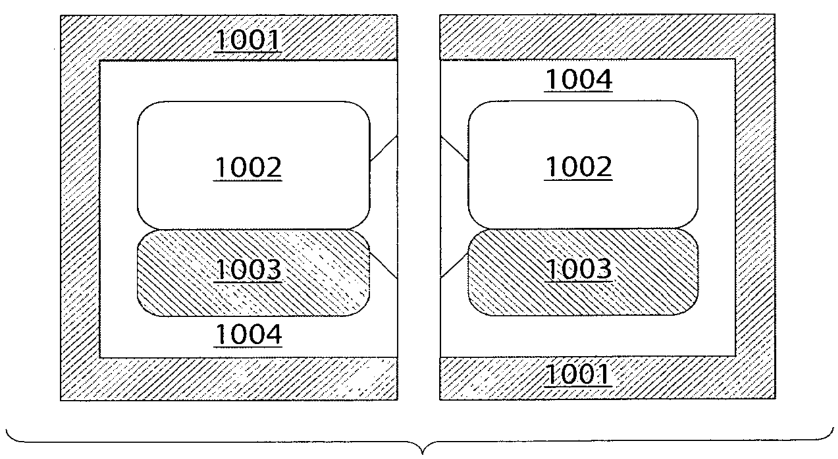


Fig. 10

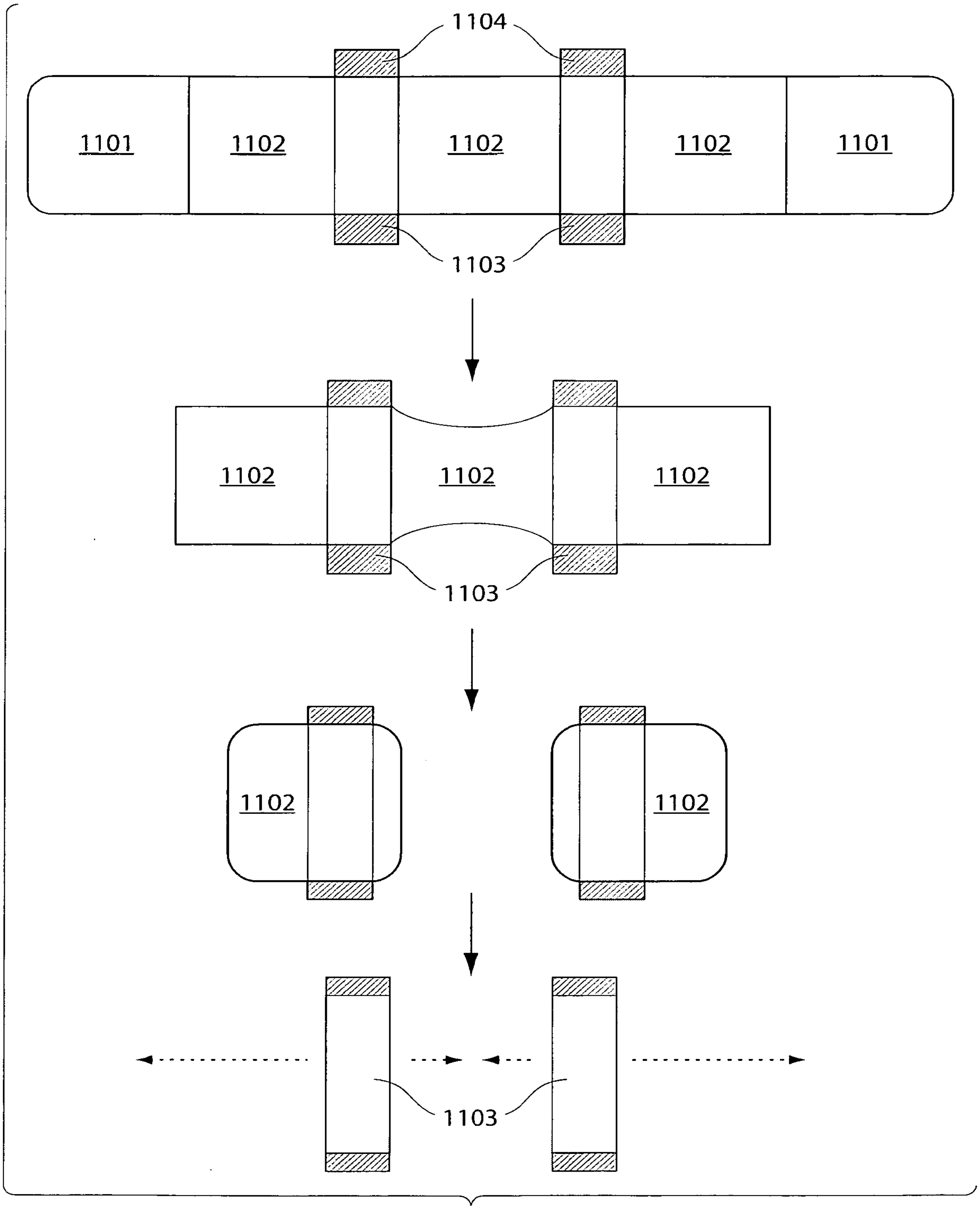

1104
1101
1102
1102
1102
1101
1103
1102
1102
1102
1103
1102
1102
1103

Fig. 11

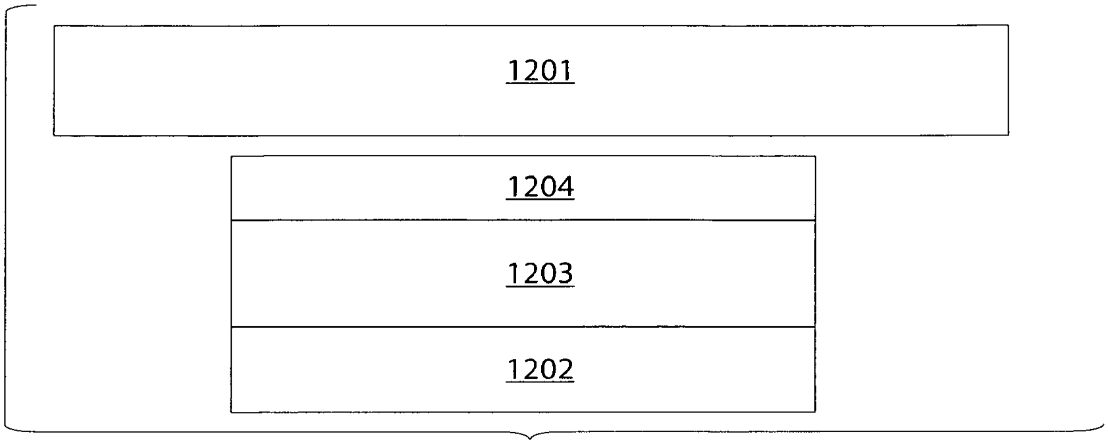


Fig. 12

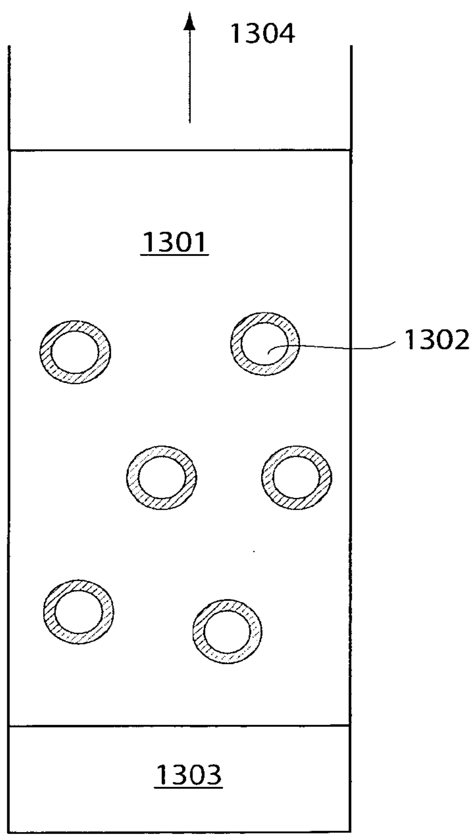


Fig. 13

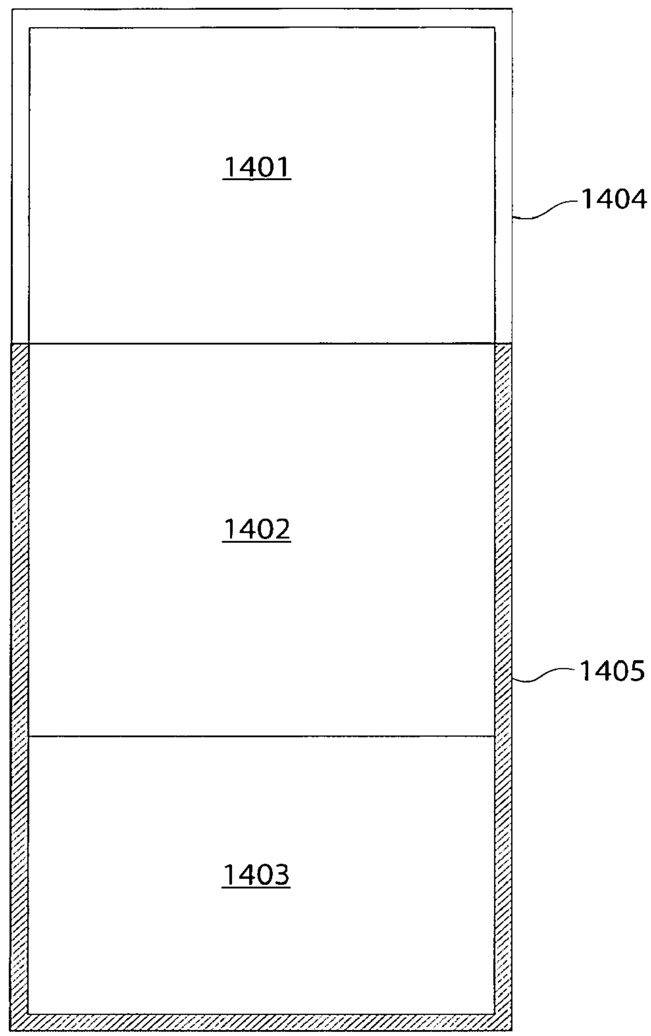


Fig. 14

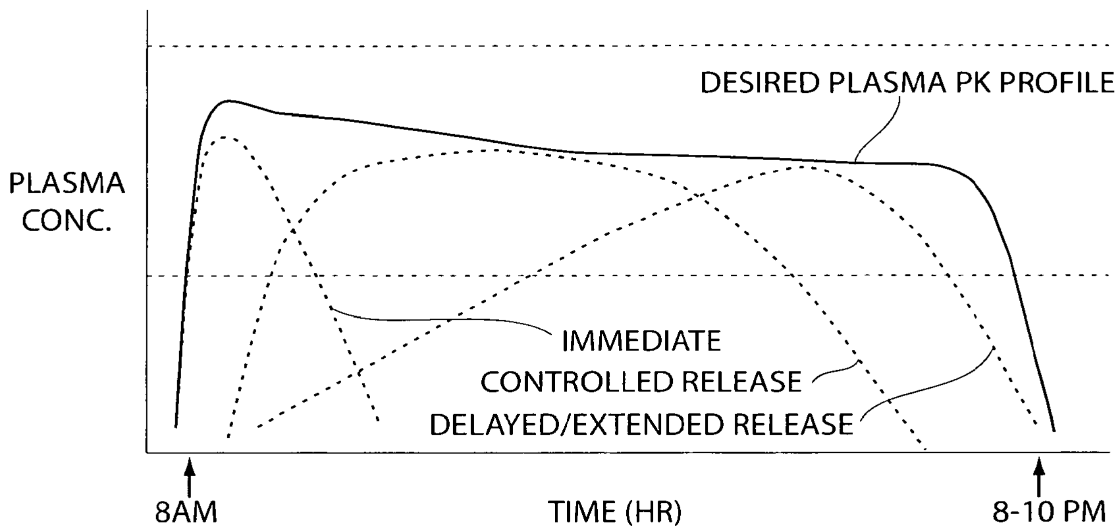

DESIRED PLASMA PK PROFILE
PLASMA CONC.
IMMEDIATE
CONTROLLED RELEASE
DELAYED/EXTENDED RELEASE
8AM
TIME (HR)
8-10 PM

Fig. 15

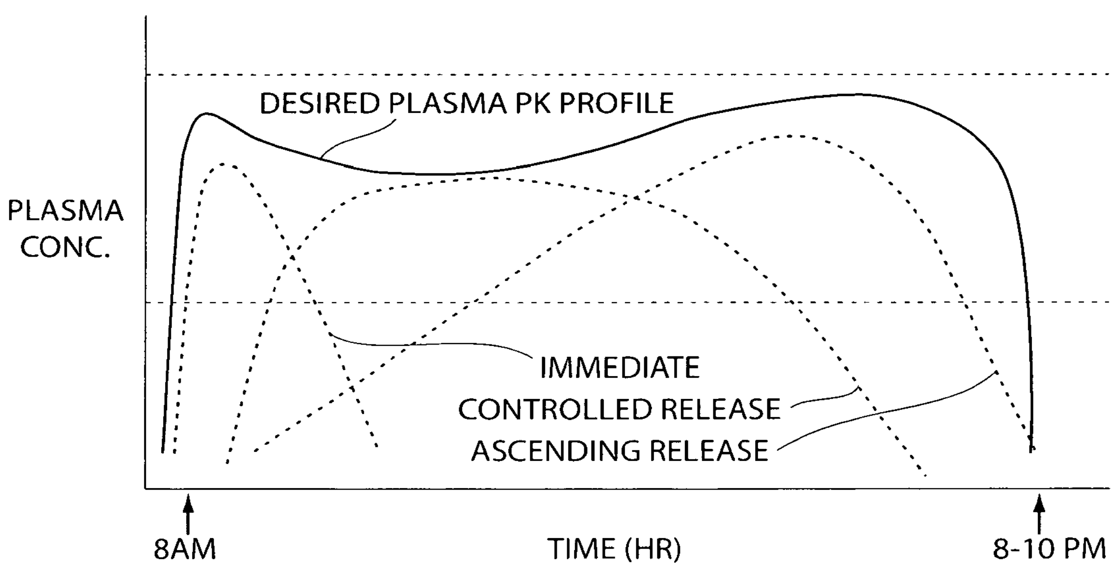

DESIRED PLASMA PK PROFILE
PLASMA CONC.
IMMEDIATE
CONTROLLED RELEASE
ASCENDING RELEASE
8AM
TIME (HR)
8-10 PM

Fig. 16

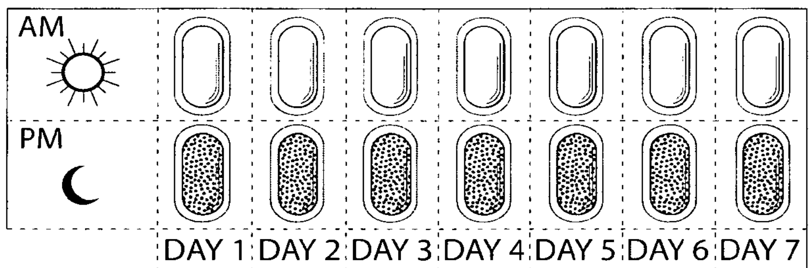


Fig. 17

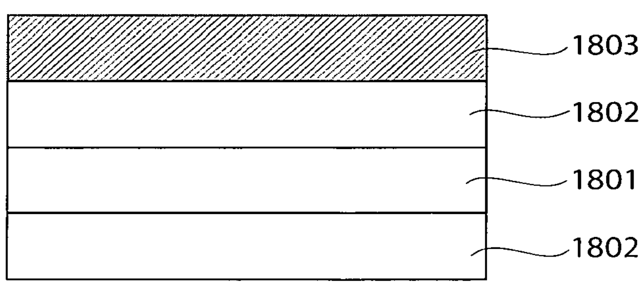


Fig. 18

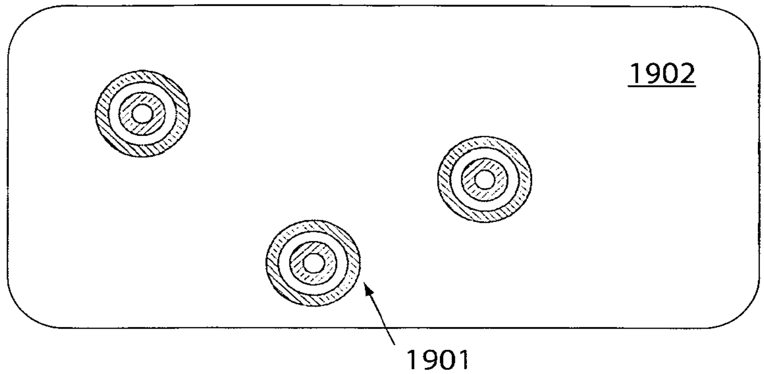


Fig. 19

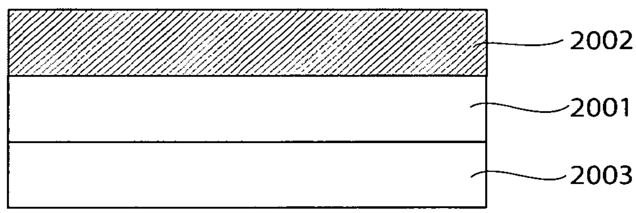


Fig. 20

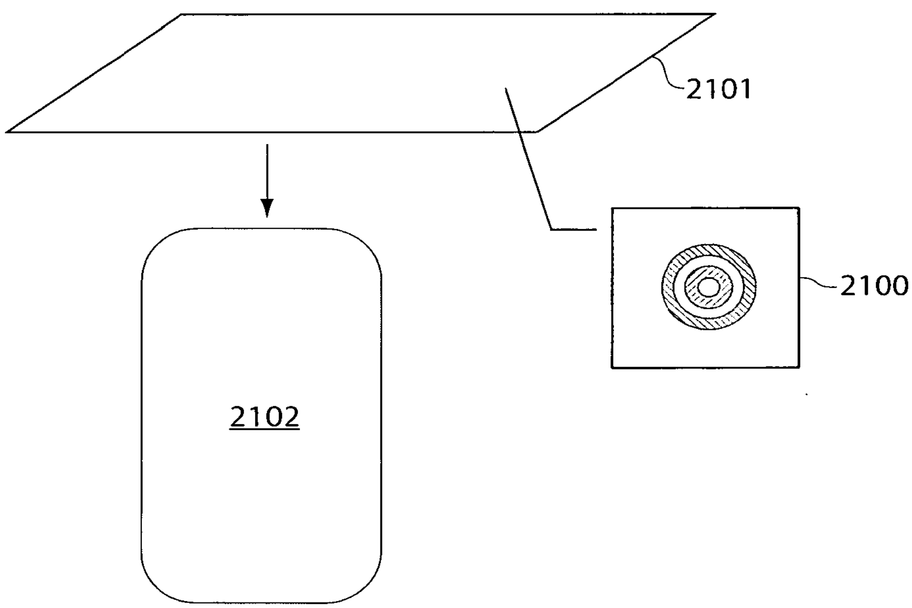


Fig. 21

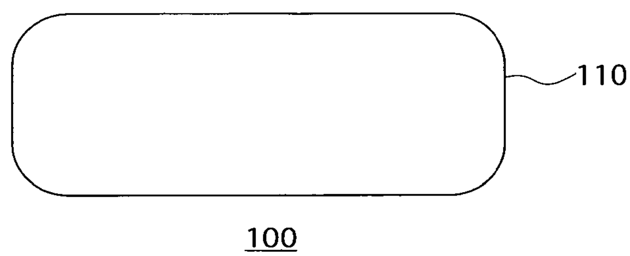


Fig. 22

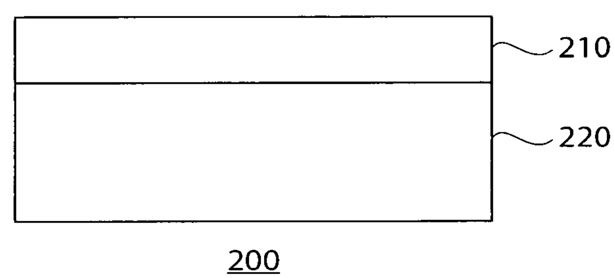


Fig. 23

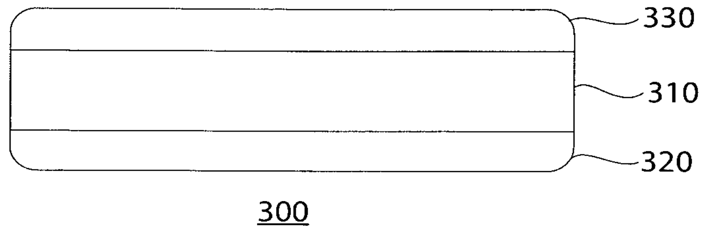


Fig. 24

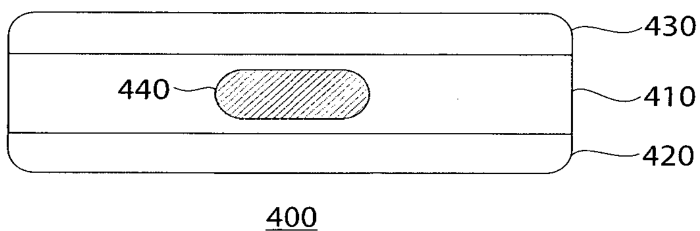


Fig. 25

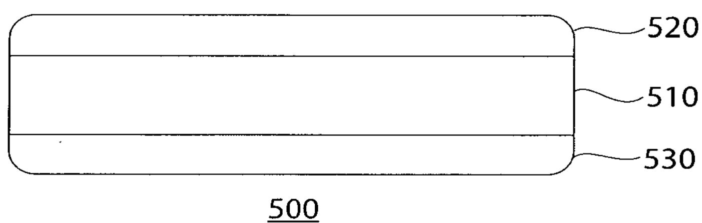


Fig. 26

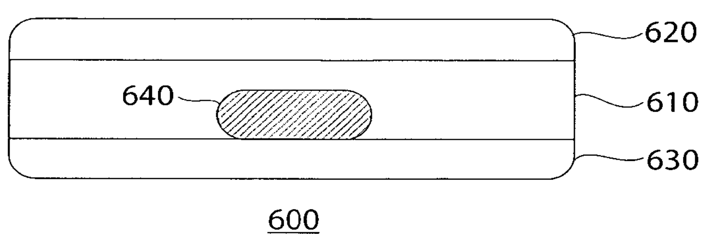
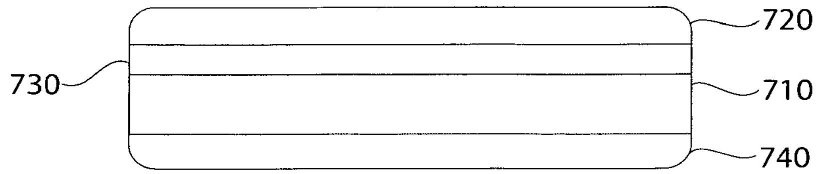
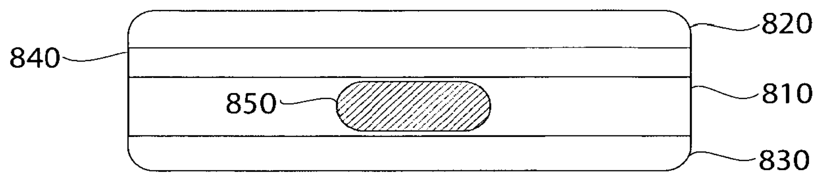


Fig. 27



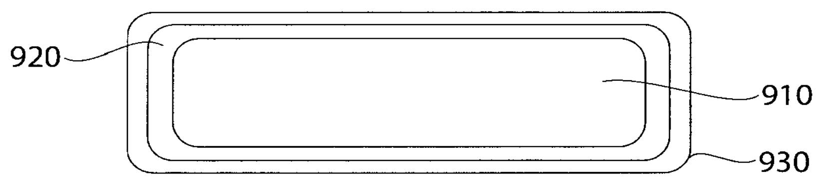
700

Fig. 28



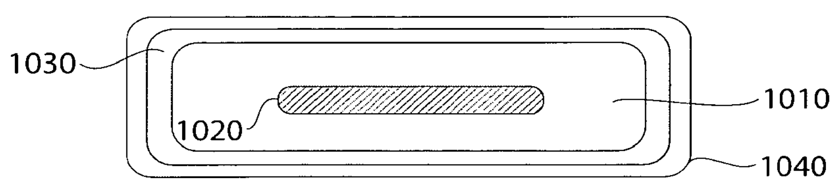
800

Fig. 29



900

Fig. 30



1000

Fig. 31

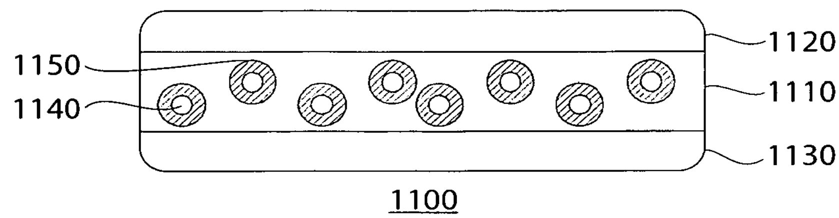


Fig. 32

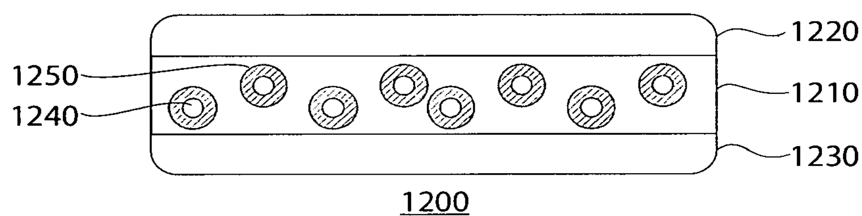


Fig. 33

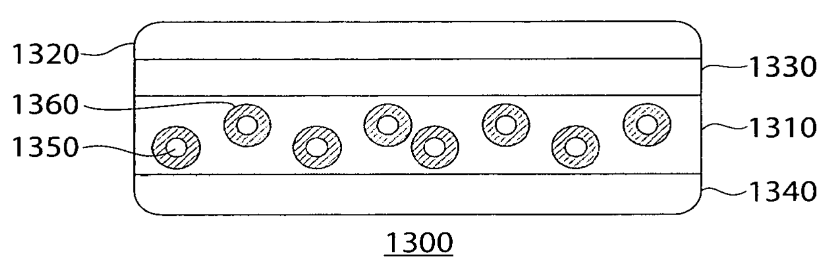


Fig. 34

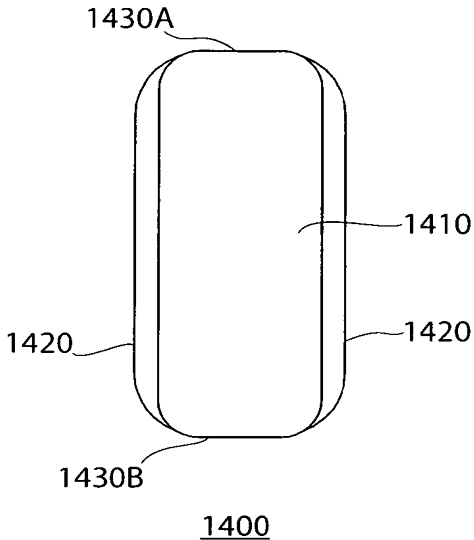


Fig. 35

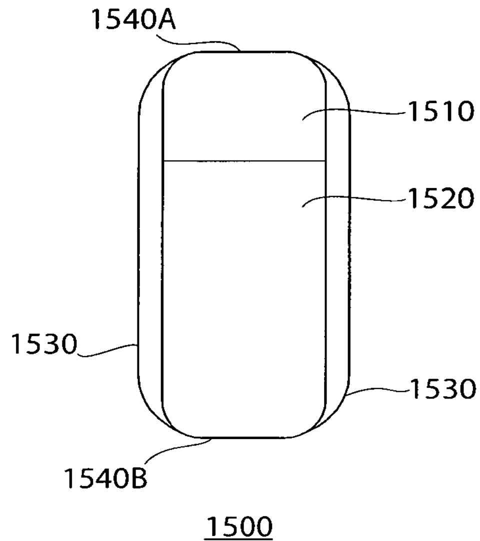


Fig. 36

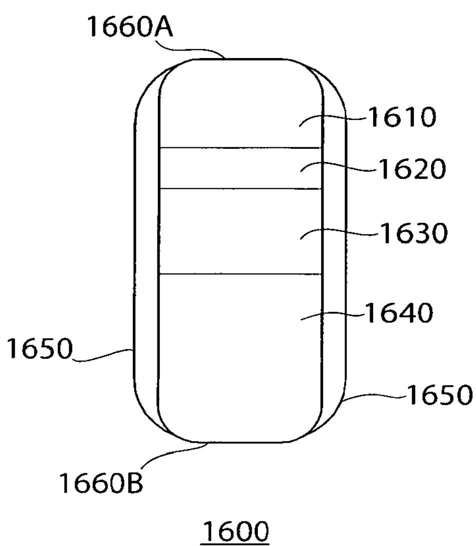


Fig. 37

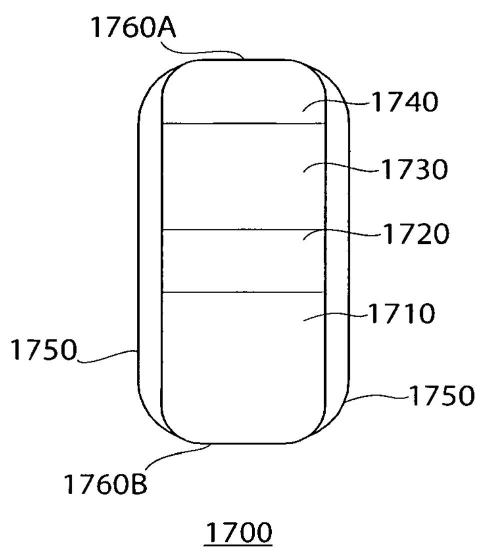
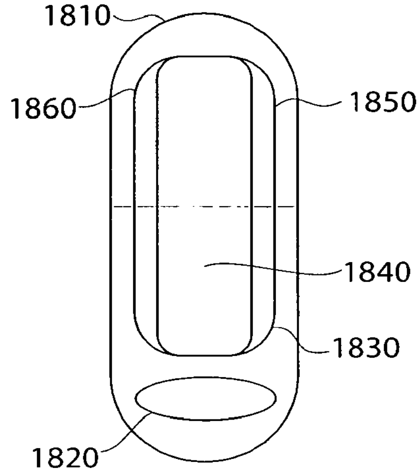
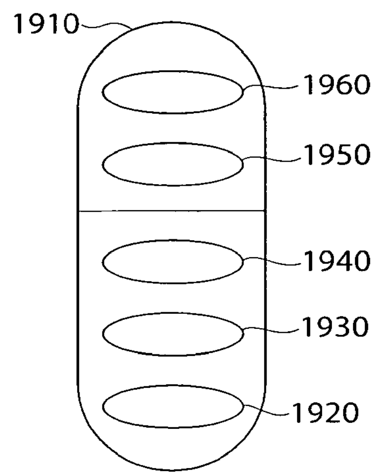


Fig. 38



1800

Fig. 39



1900

Fig. 40

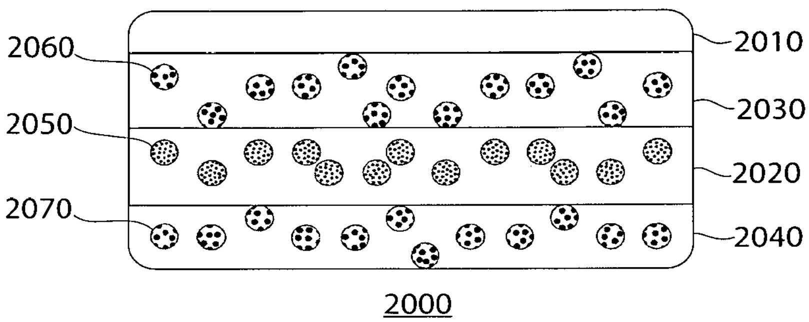


Fig. 41

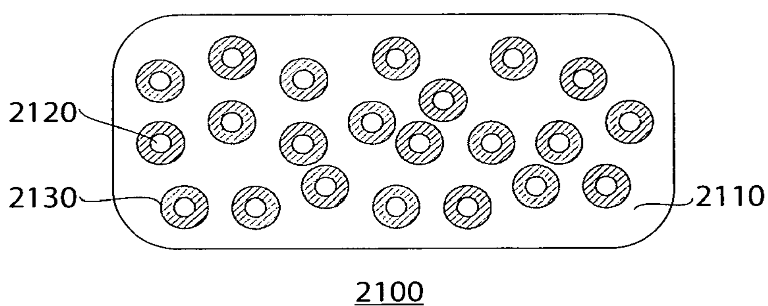


Fig. 42

PLASMA CONCENTRATION PROFILES
OF LEVODOPA AND CARBIDOPA IN FED BEAGLES FOR
SINEMET CR 50-200 TABLETS, LOT # N4682

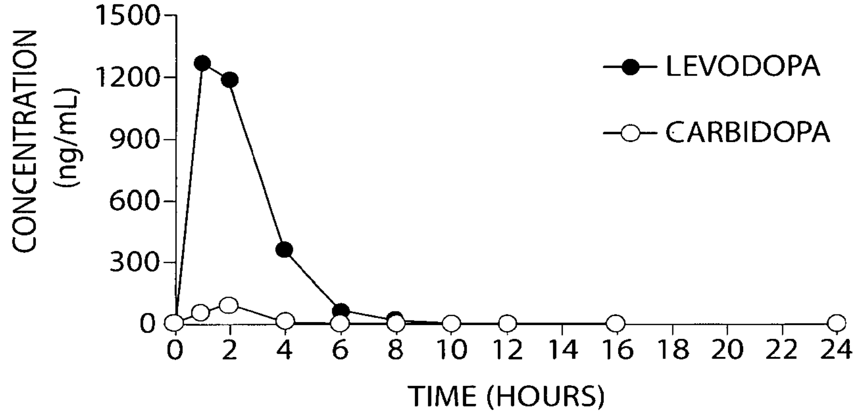


Fig. 43

IN VITRO RELEASE OF LEVODOPA AND CARBIDOPA FROM BIOADHESIVE
LEVODOPA-CARBIDOPA 200 mg/50 mg QUADRILAYER TABLETS
LOT 603-243

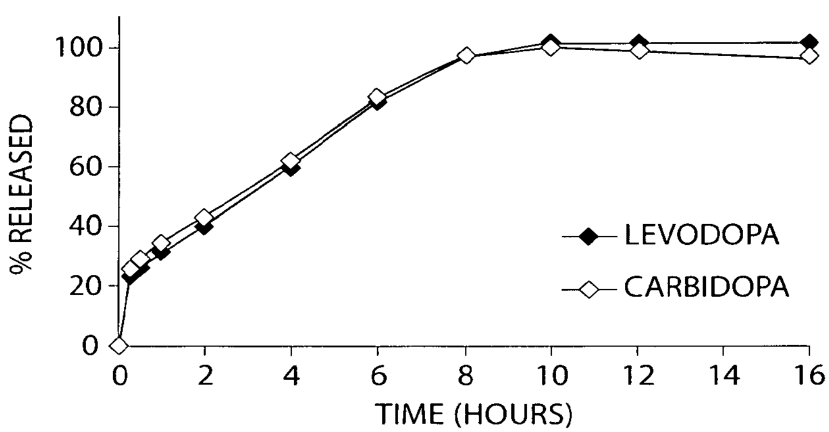


Fig. 44

PLASMA CONCENTRATION PROFILES OF LEVODOPA & CARBIDOPA IN FED BEAGLES FOR LEVODOPA-CARBIDOPA 200 mg/50 mg QUADRILAYER TABLETS, LOT 603-243

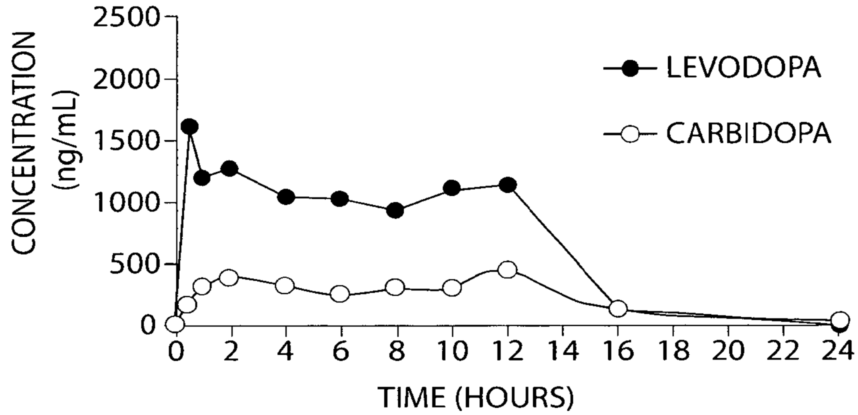


Fig. 45

PLASMA CONCENTRATION PROFILES OF LEVODOPA & CARBIDOPA IN FASTED BEAGLES FOR LEVODOPA-CARBIDOPA 200 mg/50 mg QUADRILAYER TABLETS, LOT 603-243

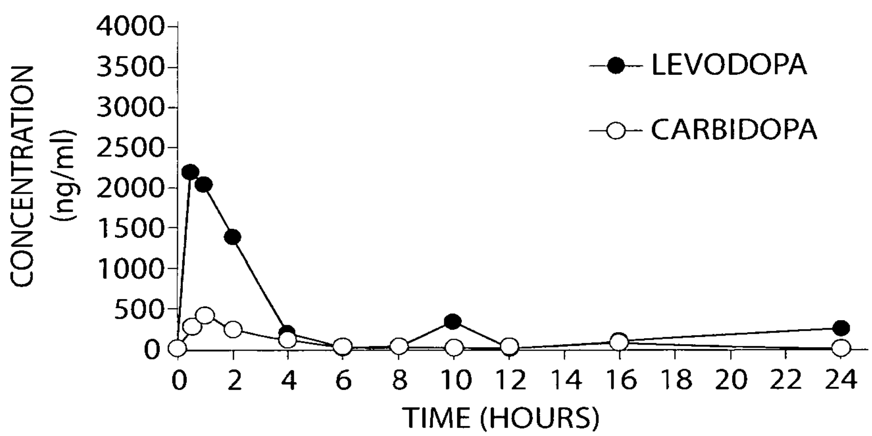


Fig. 46

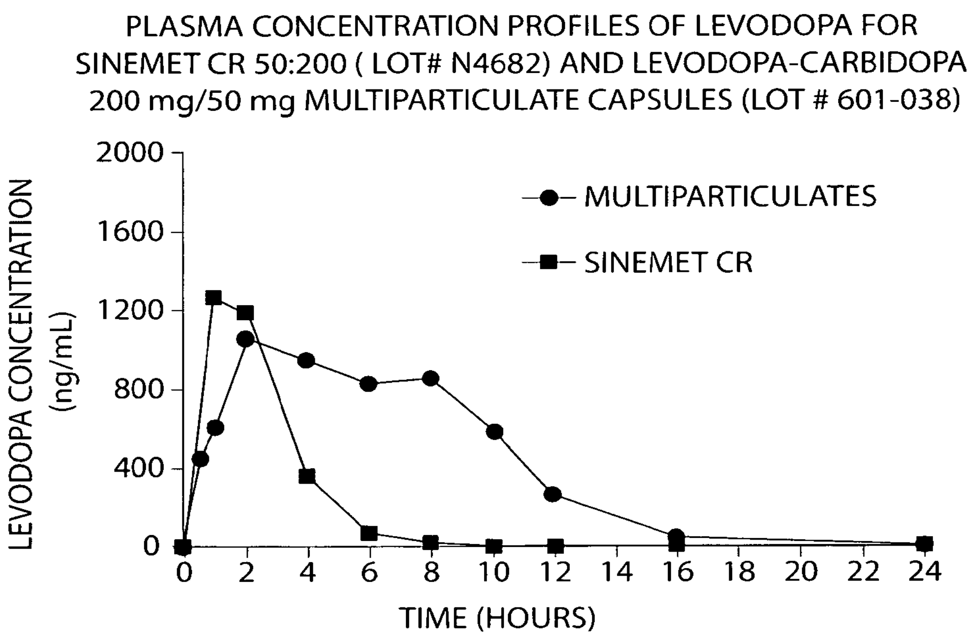

PLASMA CONCENTRATION PROFILES OF LEVODOPA FOR SINEMET CR 50:200 (LOT# N4682) AND LEVODOPA-CARBIDOPA 200 mg/50 mg MULTIPARTICULATE CAPSULES (LOT # 601-038)
MULTIPARTICULATES
SINEMET CR
LEVODOPA CONCENTRATION (ng/mL)
0
400
800
1200
1600
2000
0 2 4 6 8 10 12 14 16 18 20 22 24
TIME (HOURS)

Fig. 47

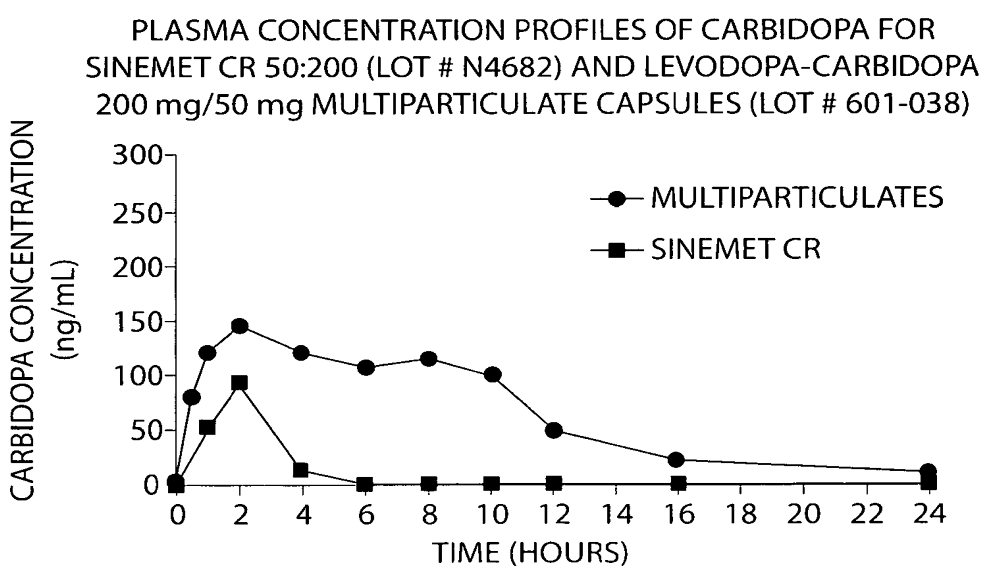

PLASMA CONCENTRATION PROFILES OF CARBIDOPA FOR SINEMET CR 50:200 (LOT # N4682) AND LEVODOPA-CARBIDOPA 200 mg/50 mg MULTIPARTICULATE CAPSULES (LOT # 601-038)
MULTIPARTICULATES
SINEMET CR
CARBIDOPA CONCENTRATION (ng/mL)
0
50
100
150
200
250
300
0 2 4 6 8 10 12 14 16 18 20 22 24
TIME (HOURS)

Fig. 48

IN VITRO RELEASE OF LEVODOPA AND CARBIDOPA FROM SINEMET CR 50:200 TABLETS, LOT # N4682

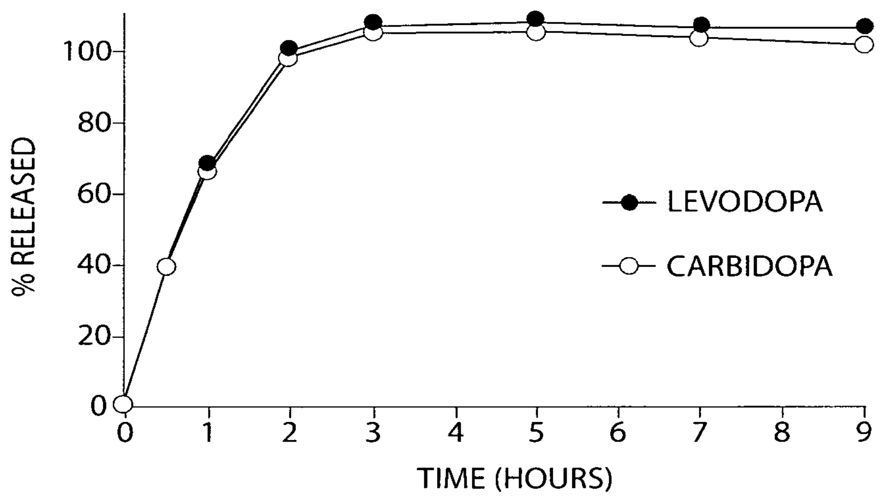


Fig. 49

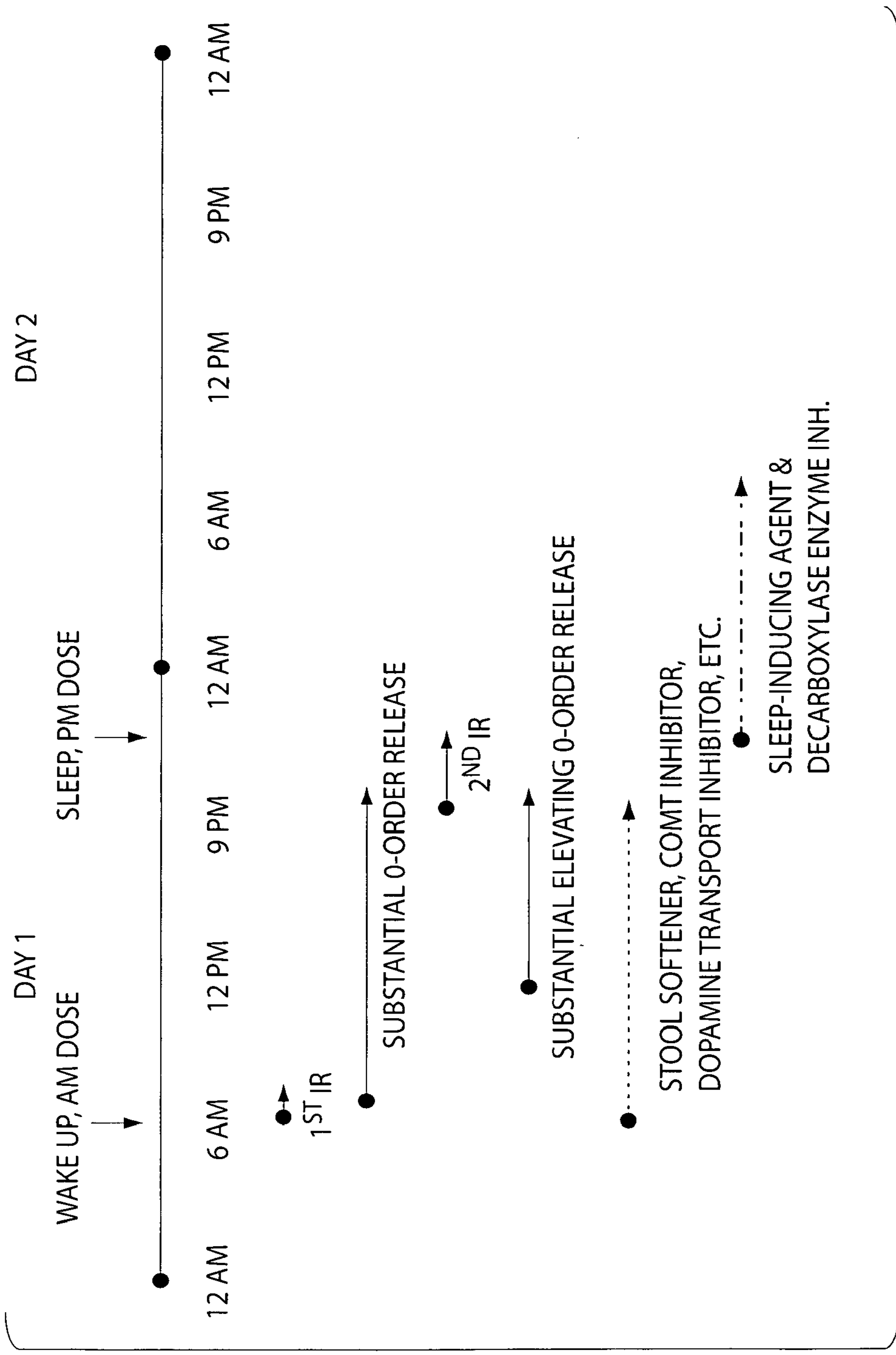

DAY 1
DAY 2
WAKE UP, AM DOSE
SLEEP, PM DOSE
12 AM
6 AM
12 PM
9 PM
12 AM
6 AM
12 PM
9 PM
12 AM
1^{ST} IR
SUBSTANTIAL 0-ORDER RELEASE
2^{ND} IR
SUBSTANTIAL ELEVATING 0-ORDER RELEASE
STOOL SOFTENER, COMT INHIBITOR,
DOPAMINE TRANSPORT INHIBITOR, ETC.
SLEEP-INDUCING AGENT &
DECARBOXYLASE ENZYME INH.

Fig. 50

IN VITRO DISSOLUTION OF CARBIDOPA 100 mg TRILAYER
XR TABLETS IN 0.1N HCl AND PBS, pH 4.5
LOT 607-015

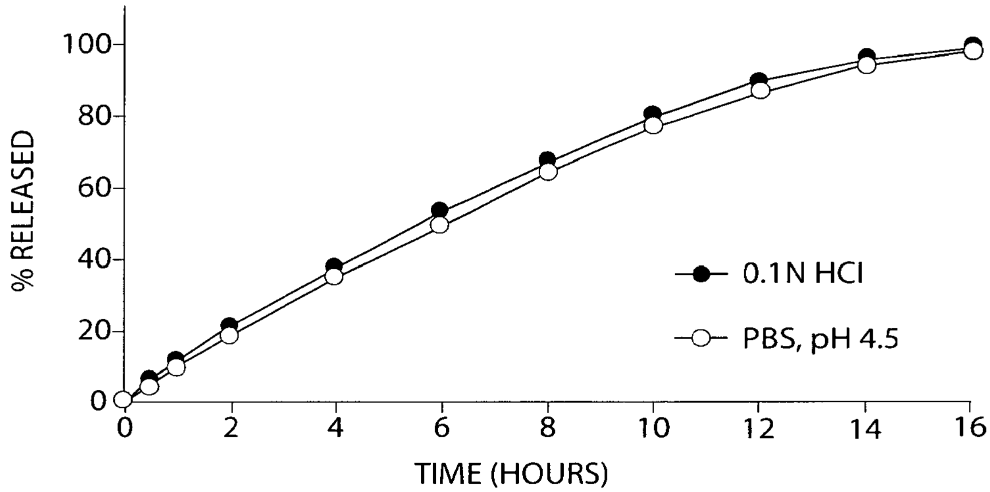


Fig. 51

IN VITRO DISSOLUTION OF CARBIDOPA 100 mg TRILAYER
XR TABLETS IN 0.1N HCl AND PBS, pH 4.5
LOT 607-016

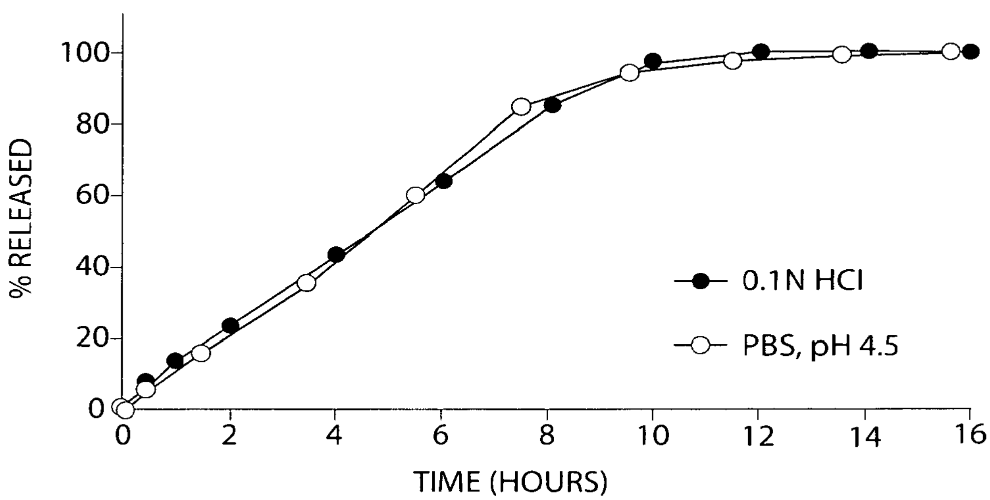


Fig. 52

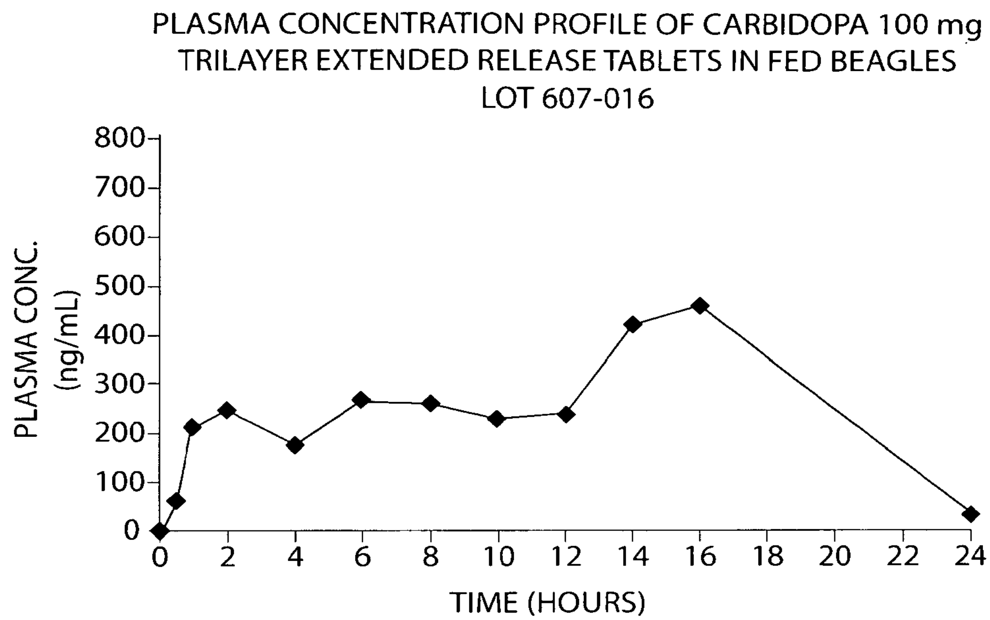

PLASMA CONCENTRATION PROFILE OF CARBIDOPA 100 mg
TRILAYER EXTENDED RELEASE TABLETS IN FED BEAGLES
LOT 607-016
PLASMA CONC. (ng/mL)
0
100
200
300
400
500
600
700
800
TIME (HOURS)
0
2
4
6
8
10
12
14
16
18
20
22
24

Fig. 53

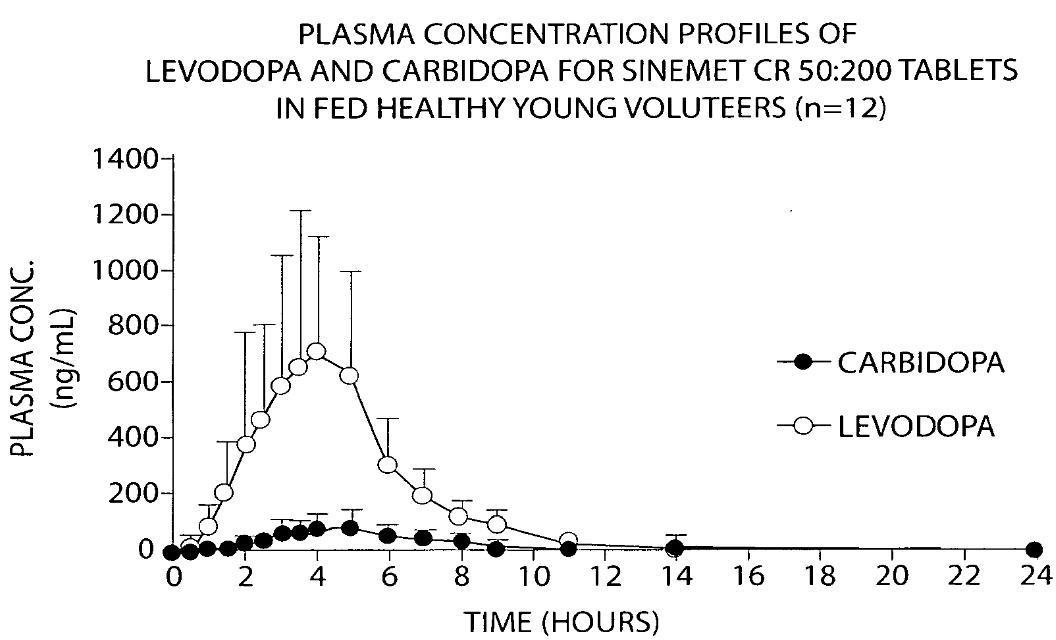

PLASMA CONCENTRATION PROFILES OF
LEVODOPA AND CARBIDOPA FOR SINEMET CR 50:200 TABLETS
IN FED HEALTHY YOUNG VOLUTEERS (n=12)
PLASMA CONC. (ng/mL)
0
200
400
600
800
1000
1200
1400
CARBIDOPA
LEVODOPA
TIME (HOURS)
0
2
4
6
8
10
12
14
16
18
20
22
24

Fig. 54

PLASMA CONCENTRATION OF LEVODOPA & CARBIDOPA IN FED HEALTHY YOUNG VOLUNTEERS FOR LEVODOPA-CARBODOPA 200mg/50mg MULTILAYER EXTENDED RELEASE TABLETS (n=6)
LOT 603-245

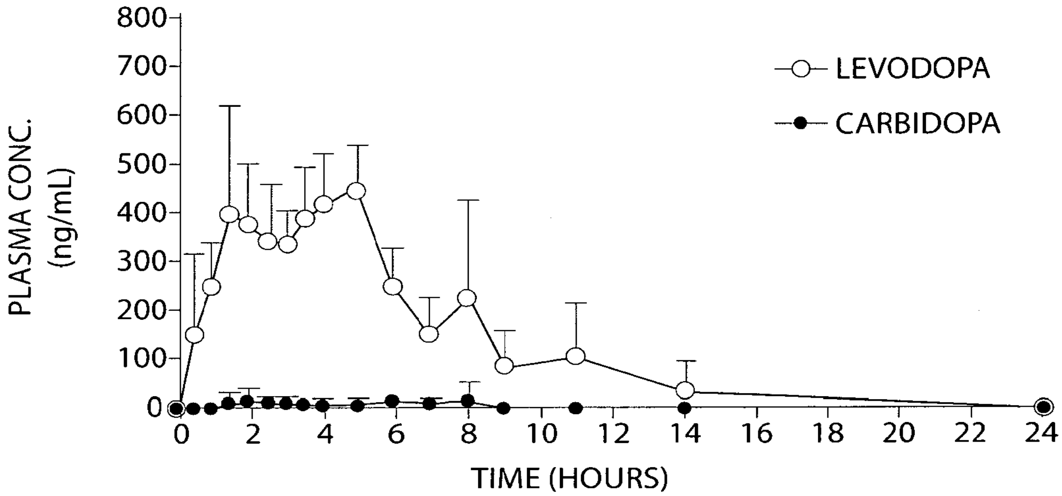


Fig. 55

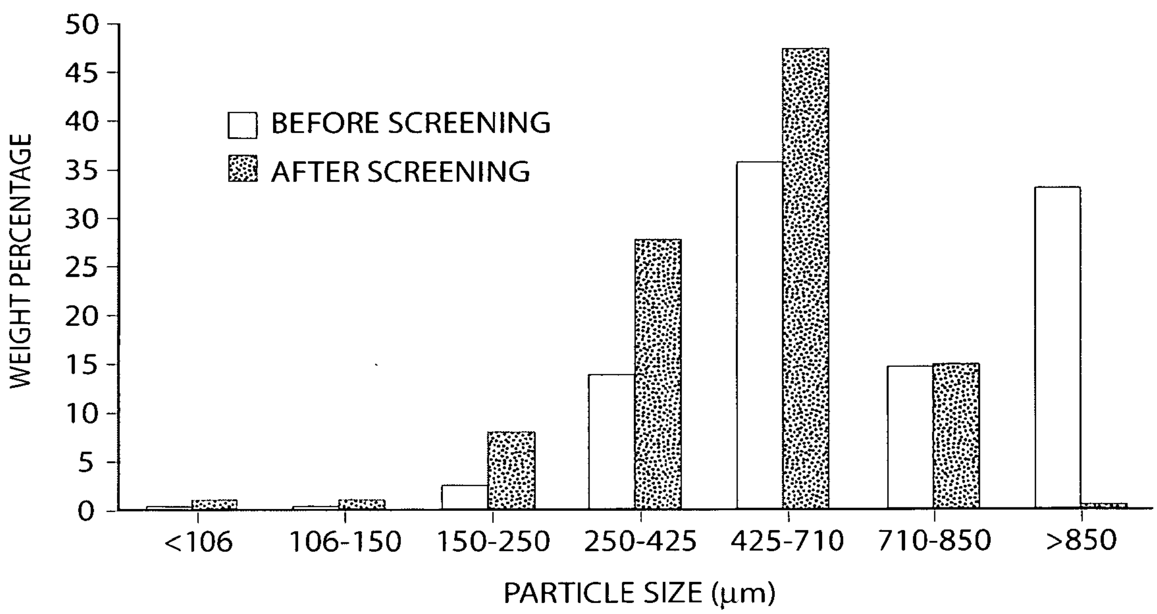


Fig. 56

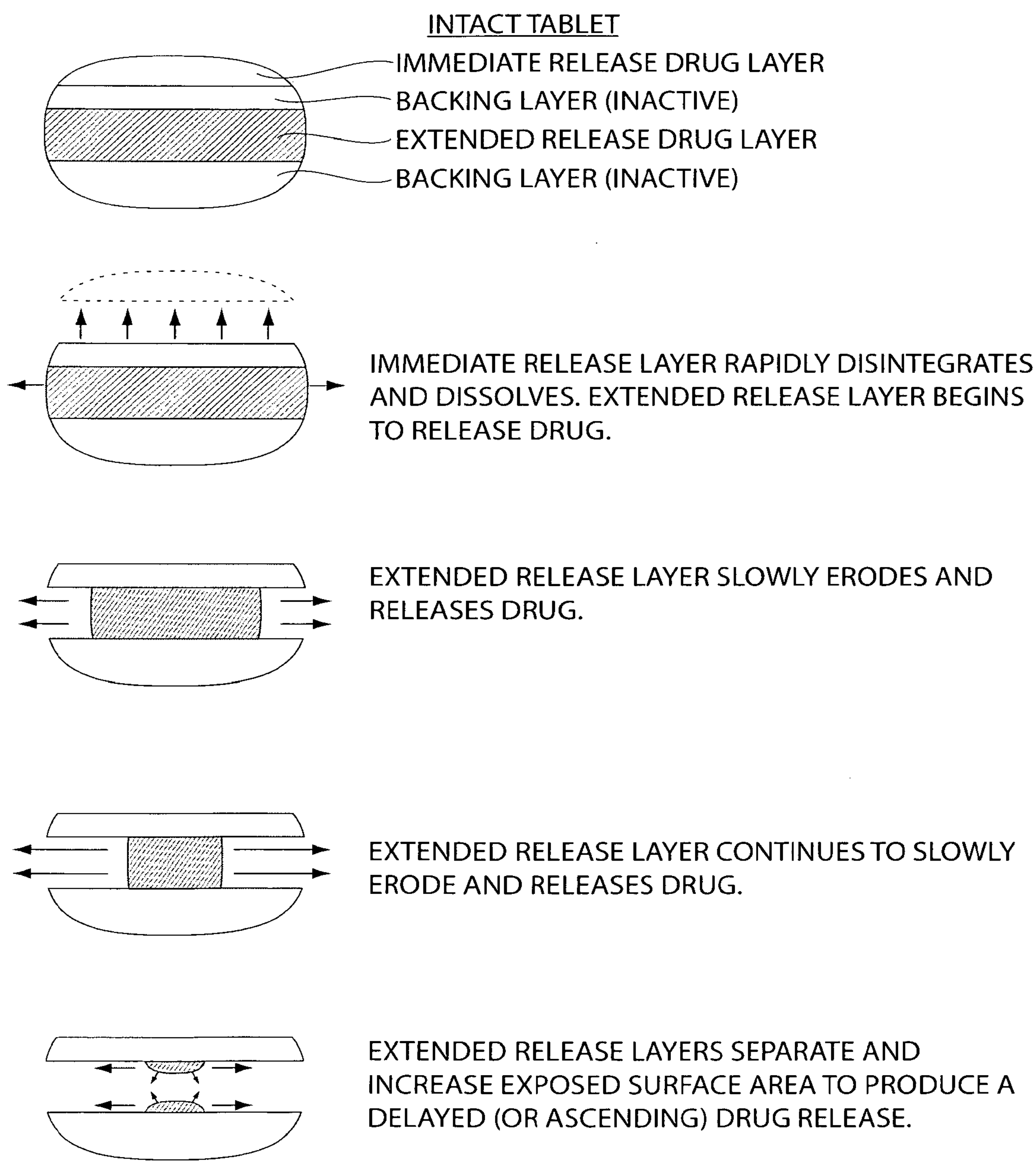
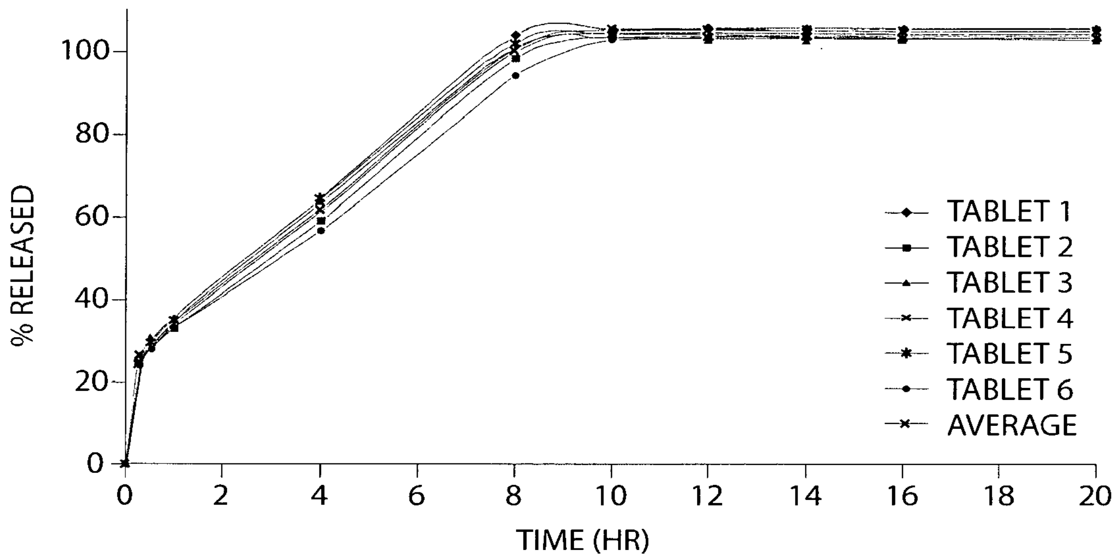
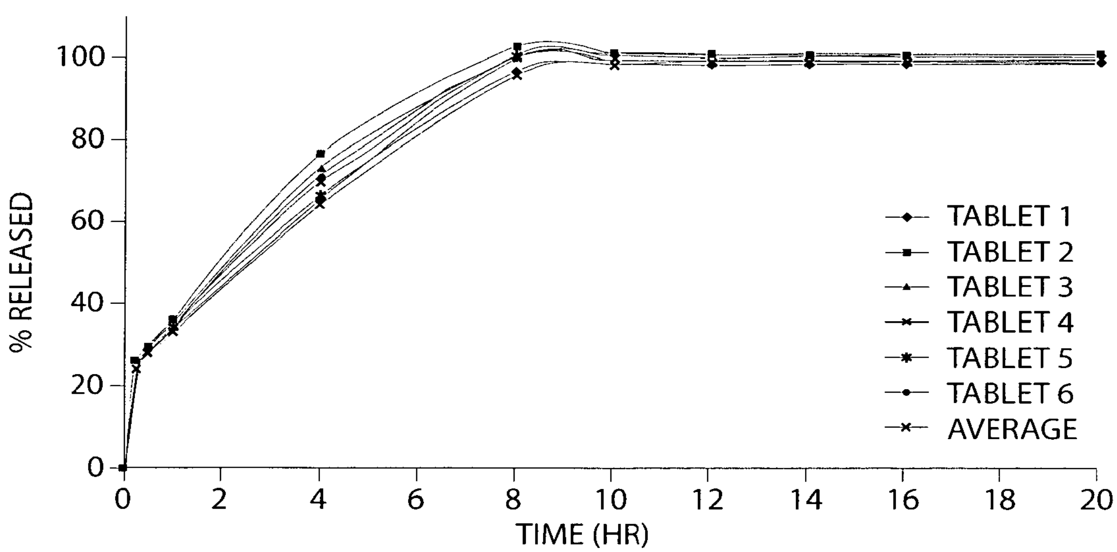

INTACT TABLET
IMMEDIATE RELEASE DRUG LAYER
BACKING LAYER (INACTIVE)
EXTENDED RELEASE DRUG LAYER
BACKING LAYER (INACTIVE)
IMMEDIATE RELEASE LAYER RAPIDLY DISINTEGRATES AND DISSOLVES. EXTENDED RELEASE LAYER BEGINS TO RELEASE DRUG.
EXTENDED RELEASE LAYER SLOWLY ERODES AND RELEASES DRUG.
EXTENDED RELEASE LAYER CONTINUES TO SLOWLY ERODE AND RELEASES DRUG.
EXTENDED RELEASE LAYERS SEPARATE AND INCREASE EXPOSED SURFACE AREA TO PRODUCE A DELAYED (OR ASCENDING) DRUG RELEASE.

Fig. 57



100
80
60
40
20
0
% RELEASED
0
2
4
6
8
10
12
14
16
18
20
TIME (HR)
TABLET 1
TABLET 2
TABLET 3
TABLET 4
TABLET 5
TABLET 6
AVERAGE

Fig. 58



100
80
60
40
20
0
% RELEASED
0
2
4
6
8
10
12
14
16
18
20
TIME (HR)
TABLET 1
TABLET 2
TABLET 3
TABLET 4
TABLET 5
TABLET 6
AVERAGE

Fig. 59